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Original Article

Fruit and vegetable intake and the risk of overall cancer in Japanese: A pooled analysis of population-based cohort studies

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ABSTRACT

Background: A series of recent reports from large-scale cohort studies involving more than 100,000 subjects reported no or only very small inverse associations between fruit and vegetable intake and overall cancer incidence, despite having sufficient power to do so. To date, however, no such data have been reported for Asian populations.
Objective: To provide some indication of the net impact of fruit and vegetable consumption on overall cancer prevention, we examined these associations in a pooled analysis of large-scale cohort studies in Japanese populations.
Methods: We analyzed original data from four cohort studies that measured fruit and vegetable consumption using validated questionnaires at baseline. Hazard ratios (HRs) in the individual studies were calculated, with adjustment for a common set of variables, and combined using a random-effects model.
Results: During 2,318,927 person-years of follow-up for a total of 191,519 subjects, 17,681 cases of overall cancers were identified. Consumption of fruit or vegetables was not associated with decreased risk of overall cancers: corresponding HRs for the highest versus lowest quartiles of intake for men and women were 1.03 (95% CI, 0.97–1.10; trend p = 1.00) and 1.03 (95% CI, 0.95–1.11; trend p = 0.97), respectively, for fruit and 1.07 (95% CI, 1.01–1.14; trend p = 0.18) and 0.98 (95% CI, 0.91–1.06; trend p = 0.99), respectively, for vegetables, even in analyses stratified by smoking status and alcohol drinking.
Conclusions: The results of this pooled analysis do not support inverse associations of fruit and vegetable consumption with overall cancers in the Japanese population.

Introduction

Cancer is the leading cause of death in many parts of the world. Fruit and vegetable consumption has long been considered to

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protect against a number of respiratory and digestive cancers.[1] However, associations with overall cancers in previous prospective cohort studies of fruit and vegetable consumption in relation to the risk of overall cancer and cardiovascular disease (CVD) simultaneously in the same population were controversial, despite comparatively clear associations for CVD.[2–8] We cannot rule out, however, the possibility that these studies might have been unable to detect smaller protective effects of fruit and vegetable intake against the risk of overall cancers: four of the seven studies included fewer than 10,000 subjects, resulting in relatively few cases of overall cancers (200–300 cases),[2–5] and the other three included more than 70,000 subjects and showed significant inverse associations between the consumption of fruit and vegetables[6–8] and risk of CVD only, and not for the risk of overall cancers.

One approach to determining the net impact of fruit and vegetable consumption on cancer prevention is to examine associations between consumption and the risk of overall cancer incidence in larger scale (e.g., more than 100,000 people, with more than 10,000 cases) cohort studies. To our knowledge, three such prospective cohort studies have been reported, and all found no[6,9] or only very small inverse associations.[10] However, these studies were all conducted in Western populations (in the United States[6,9] and Europe[10]), and no data have been reported for Asian populations. Asian populations tend to differ from Western populations with respect to the distribution of exposure (higher vegetable consumption and lower fruit consumption), outcome (higher incidence of infection-related cancers and lower incidence of hormone-related cancers), and covariates (higher prevalence of smoking and lower prevalence of obesity and low fat intake). Similar studies in Asian populations will aid characterization of the overall impact of fruit and vegetable consumption against the global burden of cancer.

In this study, we conducted a pooled analysis of larger-scale population-based cohort studies that investigated the associations of fruit and vegetable consumption with the risk of overall cancers in Japan.

Methods

Study population

In 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan initiated a pooling project using original data from major cohort studies to evaluate the association between lifestyle and major forms of cancer among Japanese.[11] To maintain the quality and comparability of data, we set inclusion criteria for the present purpose *a priori*. These included population-based cohort studies conducted in Japan; commencement in the mid-1980s to mid-1990s; more than 30,000 participants; baseline information on diet, including fruit and vegetable consumption, using a validated questionnaire; and incidence data for overall cancers during the follow-up period. We identified four studies that met these criteria: (1) the Japan Public Health Center-based Prospective Study (JPHC)-I[12]; (2) the JPHC-II[12]; (3) the Miyagi Cohort Study (MIYAGI)[13]; and (4) the Ohsaki Cohort Study (OHSAKI).[14] These studies included information on energy-adjusted consumption, which was incorporated into the main pooled analysis of the present study (based on quintiles of energy-adjusted intake). For sub-analyses based on intake frequency, two additional studies were included: (5) the Three Prefecture Study - Miyagi portion (3-pref MIYAGI)[15] and (6) the Three Prefectures Study - Aichi portion (3-pref AICHI).[15] All studies had been approved by the relevant institutional review board. Results on the associations of fruit or vegetable intake with overall cancer risk in these cohorts have been reported.[7,16] For the present analysis, we used updated data sets with extended follow-up periods.

We excluded participants with a history of cancer at baseline or missing information on all fruit and vegetable items, or with extreme energy intake (>3 standard deviations from the mean log-transformed energy intake in each study by sex, for the main analysis based on energy-adjusted quintiles). Selected characteristics of these studies are summarized in Table 1.

Follow-up

Subjects were followed from the baseline survey (JPHC-I, 1990; JPHC-II, 1993–1994; MIYAGI, 1990; OHSAKI, 1994) to the date of last follow-up for the incidence of overall cancer in each study (JPHC-I, 2006; JPHC-II, 2006; MIYAGI, 2003; OHSAKI, 2005). Residence status in each study, including survival, was confirmed through the residential registry.

Case ascertainment

In all cohorts, cancer diagnoses were identified through population-based cancer registries and active patient notification from major local hospitals. Cases were coded using the International Classification of Disease, Tenth Revision[17] or the International Classification of Diseases for Oncology, Third Edition.[18] Additional analyses restricted to smoking-related cancers as outcome were also conducted,[19] namely for cancer of the lip, oral cavity, and pharynx; esophagus; stomach; colorectum; liver; pancreas; nasal cavity and paranasal sinus; larynx; lung; uterine cervix; ovary; kidney and renal pelvis; ureter; and bladder cancer.

Exposure assessment

In each study, dietary intake was assessed using self-administered food frequency questionnaires (FFQs) on diet and various health habits (including personal medical history, smoking history, and other lifestyle factors) at baseline. Although the FFQ items, number, and categories of frequency differed by study (2 or 3 items for fruit and 5 or 6 items for vegetables), each study was able to estimate consumption in grams per day for the following food groups on the basis of frequency: fruit and vegetables, vegetables, vegetables excluding pickled vegetables, green-yellow vegetables, fruit, and fruit excluding juices. Standard portion sizes were specified for each cohort[20,21] on the basis of median values observed in dietary records obtained from subsamples. The frequency of vegetable and fruit intake was classified using four categories: almost never (JPHC-I), almost never/seldom (JPHC-II), or almost never/1–2 days/month (MIYAGI, OHSAKI, 3-pref MIYAGI, and 3-pref AICHI), 1–2 days/week, 3–4 days/week, and almost daily. For analyses based on frequency, the self-administered questionnaires of 3-pref MIYAGI and 3-pref AICHI included three vegetable and one fruit items.

Daily intake of each food item was calculated via multiplying frequency by portion size, after which intakes were calculated in g/day for total vegetables, vegetables excluding pickles, green-yellow vegetables, total fruit, and total vegetable/fruit intake. These intakes were log-transformed and adjusted for total energy intake using the residual method.[22] In contrast, for sub-analysis based on frequency, the intake frequency of each item was summed to provide a daily value and re-categorized as almost never; 1–2 days/week; 3–4 days/week, and almost daily.

Correlation coefficients (age-adjusted and de-attenuated for MIYAGI) between energy-adjusted total fruit and total vegetable intakes estimated from the FFQ and those from 12- or 28-day dietary records (DRs) were 0.55 and 0.27 among men and 0.35 and

Table 1
Characteristics of the four cohort studies included in a pooled analysis of fruits and vegetables and the risk of overall cancer incidence.

Study	Population	Age at baseline survey, years	Year(s) of baseline survey	Population size	Rate of response to baseline questionnaire, %	Method of follow-up	For the present pooled analysis							(Applied Analysis)
							Age, years	Last follow-up time	Mean duration of follow-up, years	Size of cohort		Number of overall cancer incidence		
										Men	Women	Men	Women	
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990	61,595	82%	Cancer registries and death certificates	40–59	2006	15.2	20,152 20,298	21,593 21,807	2400 2415	1681 1696	(Quintile) (Frequency)
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–1994	78,825	80%	Cancer registries and death certificates	40–69	2006	12.0	28,933 29,224	32,031 32,439	3427 3461	1990 2021	(Quintile) (Frequency)
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92%	Cancer registries and death certificates	40–64	2003	12.5	20,917 21,042	22,449 22,709	2091 2108	1381 1402	(Quintile) (Frequency)
OHSAKI	Beneficiaries of National Health Insurance among residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	54,996	95%	Cancer registries and death certificates	40–79	2005	9.0	21,777 21,980	23,667 23,976	3042 3078	1669 1691	(Quintile) (Frequency)
3-pref MIYAGI	Residents of 3 municipalities in Miyagi Prefecture, Japan	40–98	1984	31,345	94%	Cancer registries and death certificates	40–98	1992	7.5	13,080	15,377	1080	781	(Frequency)
3-pref AICHI	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985	33,529	90%	Cancer registries and death certificates	40–103	2000	11.3	15,340	17,042	1587	1122	(Frequency)
Total		40–79	1990–94	243,021	80–95		40–79	2003–06	9.0–15.2	91,779 120,964	99,740 133,350	10,960 13,729	6721 8713	(Quintile) (Frequency)

JPHC, Japan Public Health Center-based Prospective Study; MIYAGI, The Miyagi Cohort Study; OHSAKI: The Ohsaki National Health Insurance Cohort Study 3-pref MIYAGI, The Three Prefectures Study - Miyagi portion; 3-pref AICHI, The Three Prefectures Study - Aichi portion. *Sub-analysis based on frequencies of fruit and vegetable intake was independently conducted (Table 5-1 and 5-2): two cohort studies (3-pref MIYAGI and 3-pref AICHI) which were not suited for the analysis based on energy-adjusted intake because total energy intake could not be calculated from their FFQ were also included. Thus, exclusion criteria (extreme consumption according to total energy intake) in the analysis based on the frequency differed from those based on quintiles of energy-adjusted fruit and vegetable intake.

0.31 among women for the JPHC[20] and 0.76 and 0.60 among men and 0.70 and 0.45 among women for MIYAGI.[21] OHSAKI, for which information on the validation of fruit and vegetable consumption was not available (but whose population had similar cultural characteristics), utilized the same questionnaire as MIYAGI.

Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey in each study to the date of diagnosis of any cancer, migration from the study area, death, or the end of follow-up, whichever came first. In each individual study, age- (continuous) and area- (JPHC-I, JPHC-II) adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for overall cancer were estimated for the categories of energy-adjusted fruit and vegetable consumption in quintiles among men and women separately, with the lowest consumption category as the reference, using a Cox proportional hazards model. Further, linear associations were assessed using the ordinal (0–4) values for each quintile.

Further multivariate adjustments were made by including covariates in the model which were either known or suspected risk factors for cancer or had previously been found to be associated with the risk of major cancers.[1] In the multivariate model, we further adjusted for smoking status (using sex-specific covariates;

Table 2-1
Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption in Japanese men, 1990–2006.

	Lowest	Second	Third	Fourth	Highest	p for trend	p for heterogeneity	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		for the highest category	for trend
Total fruit and vegetables								
Number of subjects	18,354	18,358	18,355	18,358	18,354			
Person-years	217,070	218,667	218,957	217,783	214,059			
Number of cases	2081	2091	2152	2288	2348			
ASR (per 100,000)	1120	1110	1084	1082	1080			
HR1	1.0 (Ref.)	0.98 (0.92, 1.04)	0.95 (0.88, 1.03)	0.95 (0.90, 1.01)	0.95 (0.89, 1.00)	*0.25*	0.91	0.74
HR2	1.0 (Ref.)	1.01 (0.95, 1.07)	1.00 (0.93, 1.07)	1.03 (0.96, 1.09)	1.04 (0.98, 1.11)	*0.54*	0.96	0.78
HR3	1.0 (Ref.)	0.97 (0.91, 1.03)	1.00 (0.93, 1.08)	1.04 (0.97, 1.11)	1.04 (0.97, 1.11)	*0.77*	0.99	0.78
Fruits								
Number of subjects	18,354	18,358	18,355	18,358	18,354			
Person-years	217,028	217,845	218,569	218,887	214,208			
Number of cases	2218	2143	2156	2130	2313			
ASR (per 100,000)	1160	1117	1108	1022	1075			
HR1	1.0 (Ref.)	0.96 (0.90, 1.02)	0.94 (0.88, 1.01)	0.88 (0.81, 0.95)	0.92 (0.86, 0.97)	*<0.01*	0.78	0.44
HR2	1.0 (Ref.)	1.01 (0.95, 1.07)	1.00 (0.94, 1.08)	0.96 (0.90, 1.02)	1.03 (0.97, 1.10)	*1.00*	0.57	0.42
HR3	1.0 (Ref.)	0.98 (0.92, 1.04)	1.01 (0.94, 1.08)	0.96 (0.89, 1.04)	1.03 (0.96, 1.10)	*1.00*	0.89	0.60
Fruits, excluding juice								
Number of subjects	18,354	18,358	18,355	18,358	18,354			
Person-years	217,320	217,056	218,160	218,274	215,726			
Number of cases	2216	2127	2043	2244	2330			
ASR (per 100,000)	1167	1152	1060	1076	1034			
HR1	1.0 (Ref.)	0.97 (0.91, 1.03)	0.90 (0.84, 0.97)	0.92 (0.85, 0.99)	0.87 (0.82, 0.93)	*<0.001*	0.58	0.52
HR2	1.0 (Ref.)	1.01 (0.95, 1.07)	0.97 (0.91, 1.03)	1.00 (0.94, 1.06)	0.99 (0.93, 1.05)	*0.96*	0.38	0.72
HR3	1.0 (Ref.)	0.99 (0.92, 1.06)	0.96 (0.90, 1.03)	0.98 (0.92, 1.05)	1.00 (0.93, 1.07)	*0.90*	0.50	0.52
Vegetables								
Number of subjects	18,354	18,358	18,355	18,358	18,354			
Person-years	217,282	218,471	218,766	218,076	213,941			
Number of cases	2016	2029	2203	2280	2432			
ASR (per 100,000)	1083	1072	1100	1092	1118			
HR1	1.0 (Ref.)	0.99 (0.93, 1.05)	1.02 (0.96, 1.08)	1.00 (0.94, 1.06)	1.02 (0.96, 1.08)	*0.94*	0.92	0.88
HR2	1.0 (Ref.)	1.00 (0.94, 1.07)	1.04 (0.98, 1.11)	1.03 (0.97, 1.09)	1.07 (1.01, 1.14)	*0.18*	0.81	0.86
HR3	1.0 (Ref.)	0.99 (0.93, 1.06)	1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	1.08 (1.01,1.15)	*0.18*	0.62	0.73
Vegetables, excluding pickles								
Number of subjects	18,354	18,358	18,355	18,358	18,354			
Person-years	217,262	219,134	218,069	218,261	213,810			
Number of cases	2025	2036	2252	2278	2369			
ASR (per 100,000)	1079	1061	1126	1107	1091			
HR1	1.0 (Ref.)	1.00 (0.94, 1.06)	1.04 (0.96, 1.13)	1.02 (0.96, 1.08)	1.02 (0.96, 1.08)	*0.93*	0.82	0.94
HR2	1.0 (Ref.)	1.02 (0.95, 1.08)	1.07 (0.997, 1.16)	1.05 (0.99, 1.12)	1.07 (1.01, 1.14)	*0.10*	0.73	0.82
HR3	1.0 (Ref.)	1.02 (0.95, 1.09)	1.08 (1.01, 1.17)	1.06 (0.98, 1.14)	1.08 (1.01, 1.15)	*0.13*	0.20	0.77
Green and yellow vegetables								
Number of subjects	18,354	18,358	18,355	18,358	18,354			
Person-years	216,692	218,424	218,289	217,287	215,844			
Number of cases	2083	2001	2157	2311	2408			
ASR (per 100,000)	956	1084	1106	1095	1059			
HR1	1.0 (Ref.)	0.96 (0.91, 1.03)	1.00 (0.94, 1.06)	0.98 (0.92, 1.04)	0.95 (0.89, 1.01)	*0.58*	0.78	0.94
HR2	1.0 (Ref.)	0.99 (0.93, 1.05)	1.02 (0.95, 1.09)	1.03 (0.97, 1.09)	1.02 (0.96, 1.08)	*0.80*	0.92	0.99
HR3	1.0 (Ref.)	0.94 (0.89, 1.01)	1.01 (0.95, 1.08)	1.04 (0.98, 1.11)	1.00 (0.94, 1.07)	*0.71*	0.86	0.85

ASR, age-standardized rate; CI, confidence interval; HR, hazard ratio.
HR1 was adjusted for age (continuous), area (for JPHC-I, JPHC-II only). HR2 and 3: further adjusted for total energy intake (quintile), smoking status (never, past, <19, 19–39, or ≥40 cigarettes/day for men), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). HR3 excluded diagnosed or deceased cases of any cancers during the first 3 years of follow-up. Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.

men: never smoker, past smoker, current smoker of 1–19, 20–39, or ≥40 cigarettes/day; women: never smoker, past smoker, or current smoker), alcohol consumption (never/former drinker, <once/week as occasional drinker, ≥once/week as regular drinker of <23, 23–46, or ≥46 g ethanol/day), body mass index (BMI) in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), quintile of total energy intake (for analysis based on quintiles), history of diabetes mellitus (yes/no), and cancer screening examination (yes/no, study-specific question as follows: ≥1 examination of chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy within the preceding year for JPHC-I; ≥1 of any kind of screening examination within the preceding year for JPHC-II; ≥1 or ≥5 examinations of chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup within the preceding 1 year or 5 years, respectively, for MIYAGI and OHSAKI). Leisure time sport (almost daily or <3–4 times/w for JPHC-I and II, ≥5 h/w or <3–4 h/w for MIYAGI and OHSAKI) was also included in the model as a sensitivity analysis. To minimize the effects of malignancy itself, the first 3 years from baseline were excluded from the risk period. An indicator term for missing data was created for each covariate. Further, we also conducted stratified analysis by smoking or drinking status among never smokers and among ever smokers, as well as among never or occasional drinkers and among

Table 2-2
Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption in Japanese women, 1990–2006.

	Lowest	Second	Third	Fourth	Highest	p for trend	p for heterogeneity	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		for the highest category	For trend
Total fruit and vegetables								
Number of subjects	19,946	19,949	19,949	19,949	19,947			
Person-years	245,257	246,517	248,367	246,836	245,414			
Number of cases	1331	1269	1313	1382	1426			
ASR (per 100,000)	579	544	552	573	583			
HR1	1.0 (Ref.)	0.95 (0.87, 1.04)	0.96 (0.88, 1.06)	1.00 (0.92, 1.08)	1.01 (0.94, 1.09)	*0.90*	0.85	0.86
HR2	1.0 (Ref.)	0.97 (0.89, 1.05)	0.98 (0.90, 1.07)	1.01 (0.94, 1.09)	1.02 (0.94, 1.10)	*0.81*	0.70	0.78
HR3	1.0 (Ref.)	0.98 (0.90, 1.07)	1.00 (0.91, 1.09)	1.03 (0.95, 1.12)	1.05 (0.96, 1.14)	*0.55*	0.41	0.52
Fruits								
Number of subjects	19,946	19,949	19,949	19,949	19,947			
Person-years	244,973	246,783	248,180	247,496	244,959			
Number of cases	1375	1278	1321	1301	1446			
ASR (per 100,000)	588	554	554	539	598			
HR1	1.0 (Ref.)	0.94 (0.87, 1.02)	0.95 (0.88, 1.03)	0.93 (0.86, 1.00)	1.02 (0.94, 1.10)	*0.99*	0.82	0.86
HR2	1.0 (Ref.)	0.95 (0.88, 1.02)	0.96 (0.89, 1.04)	0.94 (0.87, 1.01)	1.03 (0.95, 1.11)	*0.97*	0.80	0.77
HR3	1.0 (Ref.)	0.95 (0.88, 1.04)	0.99 (0.91, 1.08)	0.94 (0.85, 1.03)	1.05 (0.97, 1.14)	*0.86*	0.59	0.46
Fruits, excluding juice								
Number of subjects	19,946	19,949	19,949	19,949	19,947			
Person-years	244,709	245,699	247,885	247,934	246,163			
Number of cases	1374	1262	1327	1312	1446			
ASR (per 100,000)	589	546	563	542	592			
HR1	1.0 (Ref.)	0.94 (0.86, 1.02)	0.97 (0.90, 1.04)	0.93 (0.86, 1.00)	1.01 (0.94, 1.09)	*1.00*	0.93	0.86
HR2	1.0 (Ref.)	0.95 (0.87, 1.02)	0.98 (0.91, 1.06)	0.94 (0.86, 1.01)	1.02 (0.95, 1.10)	*0.99*	0.89	0.85
HR3	1.0 (Ref.)	0.93 (0.85, 1.02)	0.99 (0.91, 1.08)	0.93 (0.85, 1.02)	1.03 (0.94, 1.12)	*0.96*	0.91	0.68
Vegetables								
Number of subjects	19,946	19,949	19,949	19,949	19,947			
Person-years	245,417	246,791	247,663	246,524	245,995			
Number of cases	1327	1328	1274	1402	1390			
ASR (per 100,000)	576	572	539	584	563			
HR1	1.0 (Ref.)	1.00 (0.92, 1.09)	0.94 (0.87, 1.02)	1.01 (0.93, 1.10)	0.98 (0.91, 1.05)	*0.97*	0.72	0.74
HR2	1.0 (Ref.)	1.01 (0.94, 1.09)	0.95 (0.88, 1.03)	1.02 (0.94, 1.11)	0.98 (0.91, 1.06)	*0.99*	0.65	0.72
HR3	1.0 (Ref.)	1.00 (0.90, 1.12)	0.95 (0.87, 1.04)	1.04 (0.93, 1.16)	0.99 (0.91, 1.07)	*1.00*	0.54	0.63
Vegetable, excluding pickles								
Number of subjects	19,946	19,949	19,949	19,949	19,947			
Person-years	245,703	247,306	247,225	246,562	245,594			
Number of cases	1329	1313	1363	1317	1399			
ASR (per 100,000)	585	582	577	550	569			
HR1		1.00 (0.90, 1.10)	1.02 (0.94, 1.10)	0.97 (0.89, 1.04)	1.00 (0.92, 1.08)	*0.99*	0.34	0.57
HR2		1.01 (0.92, 1.11)	1.03 (0.96, 1.12)	0.98 (0.91, 1.06)	1.01 (0.92, 1.10)	*1.00*	0.28	0.50
HR3		1.01 (0.93, 1.10)	1.03 (0.95, 1.13)	0.97 (0.89, 1.06)	1.01 (0.91, 1.12)	*1.00*	0.22	0.29
Green and yellow vegetables								
Number of subjects	19,946	19,949	19,949	19,949	19,947			
Person-years	244,769	246,500	246,852	247,565	246,705			
Number of cases	1365	1286	1325	1354	1391			
ASR (per 100,000)	595	558	566	561	557			
HR1	1.0 (Ref.)	0.95 (0.88, 1.03)	0.96 (0.86, 1.08)	0.95 (0.88, 1.02)	0.95 (0.88, 1.02)	*0.64*	0.93	0.98
HR2	1.0 (Ref.)	0.96 (0.89, 1.04)	0.98 (0.86, 1.11)	0.96 (0.89, 1.04)	0.96 (0.89, 1.03)	*0.82*	0.89	0.98
HR3	1.0 (Ref.)	0.94 (0.87, 1.03)	0.98 (0.84, 1.15)	0.96 (0.89, 1.05)	0.95 (0.88, 1.04)	*0.89*	0.96	0.96

ASR, age-standardized rate; CI, confidence interval; HR, hazard ratio.
HR1 was adjusted for age (continuous), area (for JPHC-I, JPHC-II only). HR2 and 3: further adjusted for total energy intake (quintile), smoking status (never, past, or current), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). HR3 excluded diagnosed or deceased cases of any cancers during the first 3 years of follow-up. Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.

regular drinkers. These analyses were repeated for cancers associated with tobacco smoking.

A random-effects model was used to obtain a single pooled estimate of the HRs from the individual studies for each category. The study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. A study that had no cases for a category was not included in the pooled estimate for that category. The trend association was assessed in a similar manner: investigators from each study calculated the regression coefficient and its standard error of linear trend for fruit/vegetable consumption category treated as an ordinal variable. These values from the individual studies were then combined using a random-effects model.[23] We tested for and quantified the heterogeneity of the HRs for the highest category and the trend association of fruit/vegetables consumption among studies using the I^2 statistic.

All statistical analyses were conducted using SAS (Version 9.1.3, 2006, SAS Institute Inc., Cary, NC, USA) statistical software.

Results

The present study included 191,519 subjects (91,779 men and 99,740 women) and 17,681 cases of overall cancer (10,960 men and 6721 women) accumulated during 2,318,927 person-years of follow-up from four large-scale cohorts (Table 1). With regard to the variation of intakes by quintiles, cut-offs of the fourth/highest quintile of fruit or vegetable consumption were three- to five-fold or more and two- to three-fold, respectively, of those for the lowest/second quintile for each cohort.[24] In the study-specific analysis, no associations were found between fruit or vegetable consumption and the risk of overall cancer in either gender or specific cohorts in the multivariate analysis, although a significant inverse association was found for fruit consumption in JPHC-I and OHSAKI men in the age- and area-adjusted analysis (data not shown).

Among both men and women, no significant inverse associations were found between fruit or vegetable intake and the risk of overall cancer, whether combined or separated (see HR1 and HR2 in Table 2-1 and Table 2-2) (multivariate HR of highest quintiles of total fruit and vegetables vs. the lowest: 1.04; 95% CI, 0.98–1.11; trend p = 0.54 for men; and 1.02; 95% CI, 0.94–1.10; trend p = 0.81 for women). Rather, a statistically significant positive HR was found for the highest quintile of total vegetable consumption, after adjustment for potential confounders (HR2) among men (multivariate HR of highest quintile of vegetables vs. the lowest: 1.07; 95% CI, 1.01–1.14) without any significant trend association (trend p = 0.18). Fruit intake showed a small significant inverse association in age- and area-adjusted HRs among men (HR1 of highest quintile vs. the lowest: 0.92; 95% CI, 0.86–0.97; trend p < 0.01); however, the association did not remain statistically significant when adjusted for further variables (highest quintile vs. the lowest: 1.03; 95% CI, 0.97–1.10; trend p = 1.00). No specific fruit or vegetable showed significant inverse association with the risk of overall cancer. The results were not materially different in the analyses that

Table 3
Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption, stratified by smoking status, in Japanese men and women.

	Lowest	Second	Third	Fourth	Highest	p for trend	p for heterogeneity	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		for the highest category	for trend
Men (19,299 never smokers and 70,924 ever smokers)								
Fruits								
Never smokers								
Number of cases	324	344	284	364	357			
HR2	1.0 (Ref.)	1.11 (0.94, 1.3)	0.92 (0.77, 1.1)	1.08 (0.92, 1.28)	1.10 (0.93, 1.29)	*0.86*	0.88	0.88
Ever smokers								
Number of cases	1825	1736	1820	1761	1957			
HR2	1.0 (Ref.)	0.99 (0.92, 1.05)	1.01 (0.93, 1.1)	0.95 (0.89, 1.01)	1.01 (0.95, 1.08)	*1.00*	0.56	0.39
Vegetables								
Never smokers								
Number of cases	311	292	321	368	381			
HR2	1.0 (Ref.)	0.91 (0.77, 1.07)	0.96 (0.82, 1.12)	1.09 (0.93, 1.27)	1.06 (0.91, 1.24)	*0.37*	0.49	0.79
Ever smokers								
Number of cases	1650	1706	1828	1883	2032			
HR2	1.0 (Ref.)	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	1.02 (0.96, 1.09)	1.07 (1.00, 1.15)	*0.31*	0.81	0.78
Women (80,600 never smokers and 8300 ever smokers)								
Fruits								
Never smokers								
Number of cases	1084	1039	1044	1061	1153			
HR2	1.0 (Ref.)	0.97 (0.89, 1.06)	0.97 (0.89, 1.06)	0.96 (0.88, 1.04)	1.04 (0.95, 1.13)	*0.96*	0.54	0.51
Ever smokers								
Number of cases	134	119	105	122	119			
HR	1.0 (Ref.)	0.86 (0.67, 1.11)	0.86 (0.66, 1.11)	0.92 (0.69, 1.22)	0.90 (0.70, 1.15)	*0.85*	0.74	0.78
Vegetables								
Never smokers								
Number of cases	1058	1053	1014	1159	1097			
HR	1.0 (Ref.)	0.99 (0.90, 1.1)	0.94 (0.86, 1.03)	1.03 (0.95, 1.12)	0.96 (0.87, 1.05)	*0.98*	0.35	0.91
Ever smokers								
Number of cases	108	132	121	109	129			
HR	1.0 (Ref.)	1.19 (0.93, 1.53)	1.07 (0.78, 1.47)	0.93 (0.64, 1.37)	1.10 (0.85, 1.42)	*1.00*	0.75	0.53

Hazard ratios were adjusted for age (continuous), area (for JPHC-I, JPHC-II only), total energy intake (quintile), smoking status (never, past, <19, 19–39, or ≥40 cigarette/day for men; never, past, or current for women), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.

further adjusted for leisure time sport (data not shown), excluded cancer screening examinations from adjustment factors (data not shown), or excluded cases of cancer diagnosed during the first 3 years of follow-up (HR3).

Further, these results did substantially change in analyses that used sub-tertiles of the lowest quintile of total fruit and vegetable consumption and highest quintile as reference category: the multivariate HR for the lowest sub-tertile of the lowest quintile versus the highest quintile of consumption for men and women was 0.89 (95% CI, 0.77–1.02; trend p = 0.35) and 1.01 (95% CI, 0.92–1.10; trend p = 0.95), respectively.

In stratified analysis by smoking status or alcohol drinking, no significant inverse association was found between fruit or vegetable intake and the risk of overall cancer, whether combined or separated both among men and women (Table 3 and Table 4). A significant positive HR was found for the highest quintile of vegetables (1.07; 95% CI, 1.00–1.15), without a significant trend association (trend p = 0.31), among male smokers. However, no associations were found between fruit or vegetable consumption and smoking-related cancers in either gender: multivariate HRs of the highest quartile of fruit or vegetable intake versus the lowest were 1.02 (95% CI, 0.95–1.09) and 1.05 (95% CI, 0.98–1.12), respectively, among men (trend p = 1.00 and 0.56, respectively) and 1.0 (95% CI, 0.91–1.10) and 0.98 (95% CI, 0.85–1.12), respectively, among women (trend p = 1.00 for both).

In a sub-analysis based on intake frequency, which included the two added cohort studies, with a total of 254,314 subjects (120,964 men and 133,350 women) and 22,442 cases of overall cancer (13,729 men and 8713 women), no association was again found between fruit or vegetable consumption and overall cancer risk among either gender (Table 5-1 and Table 5-2): corresponding multivariate HRs of almost daily versus almost never were 1.02 (95% CI, 0.96–1.08) and 0.99 (95% CI, 0.89–1.11), respectively, for men (trend p = 1.00 and 0.95, respectively), and 0.95 (95% CI, 0.88–1.02) and 0.92 (95% CI, 0.72–1.18), respectively, for women (trend p = 1.00 for both). Further, no specific fruit or vegetable showed a significant inverse association with the risk of overall cancer. Moreover, no significant inverse association was found between fruit or vegetable intake and the risk of smoking-related cancer for either gender (data not shown).

Discussion

This pooled analysis of major population-based cohort studies in Japan, which included data on 17,681 cancer cases, revealed no significant inverse associations of fruit or vegetable consumption with the risk of overall cancer, whether combined or separated by specific groups. Further, these results did not substantially change in stratified analyses by smoking status or alcohol drinking. Moreover, no significant inverse associations were shown when outcomes were confined to smoking-related cancers. To our knowledge, this pooled analysis included the largest number of overall cancer cases in an Asian population to date.

Table 4
Pooled analysis of overall cancer incidence according to quintile of fruit and vegetable consumption, stratified by alcohol drinking, in Japanese men and women.

	Lowest	Second	Third	Fourth	Highest	p for trend	p for heterogeneity	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		for the highest category	For trend
Men (29,057 non-drinkers or occasional drinkers and 59,737 drinkers)								
Fruits								
Non-drinkers or occasional drinkers								
Number of cases	693	634	665	702	790			
HR2	1.0 (Ref.)	0.95 (0.77, 1.16)	0.95 (0.79, 1.13)	0.98 (0.88, 1.09)	1.06 (0.95, 1.17)	*0.51*	0.88	0.86
Drinkers								
Number of cases	1460	1384	1436	1348	1458			
HR2	1.0 (Ref.)	1.00 (0.89, 1.11)	1.04 (0.97, 1.12)	0.93 (0.87, 1.01)	1.00 (0.93, 1.08)	*0.95*	0.60	0.22
Vegetables								
Non-drinkers or occasional drinkers								
Number of cases	639	638	687	726	794			
HR2	1.0 (Ref.)	1.01 (0.91, 1.13)	1.03 (0.92, 1.15)	1.00 (0.90, 1.12)	1.11 (0.998, 1.23)	*0.39*	0.55	0.73
Drinkers								
Number of cases	1301	1289	1436	1500	1560			
HR2	1.0 (Ref.)	0.97 (0.90, 1.05)	1.04 (0.97, 1.12)	1.03 (0.96, 1.11)	1.05 (0.97, 1.13)	*0.29*	0.45	0.46
Women (79,055 nondrinkers or occasional drinkers and 11,369 drinkers)								
Fruits								
Non-drinkers or occasional drinkers								
Number of cases	1129	1042	1068	1074	1142			
HR2	1.0 (Ref.)	0.93 (0.86, 1.02)	0.95 (0.87, 1.04)	0.94 (0.86, 1.02)	0.99 (0.91, 1.08)	*1.00*	0.58	0.45
Drinkers								
Number of cases	127	115	118	132	144			
HR2	1.0 (Ref.)	1.01 (0.70, 1.45)	0.96 (0.74, 1.24)	1.11 (0.84, 1.45)	1.16 (0.90, 1.49)	*0.69*	0.74	0.72
Vegetables								
Non-drinkers or occasional drinkers								
Number of cases	1078	1074	1031	1152	1120			
HR2	1.0 (Ref.)	0.97 (0.84, 1.13)	0.94 (0.86, 1.02)	1.01 (0.91, 1.11)	0.99 (0.87, 1.13)	*0.98*	0.20	0.92
Drinkers								
Number of cases	128	121	121	132	134			
HR2	1.0 (Ref.)	0.97 (0.75, 1.24)	0.94 (0.73, 1.21)	1.06 (0.83, 1.36)	0.97 (0.76, 1.25)	*1.00*	0.40	0.17

Hazard ratios were adjusted for age (continuous), area (for JPHC-I, JPHC-II only), total energy intake (quintile), smoking status (never, past, <19, 19–39, or ≥40 cigarette/day for men; never, past, or current for women), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.

Table 5-1
Pooled analysis of total cancer incidence according to frequency of fruit and vegetable intake among 120,964 Japanese men, 1990–2006.

	Almost never	1-2/week	3-4/week	Almost daily	p for trend	p for heterogeneity	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		for the highest category	For trend
Total fruit and vegetables							
Number of subjects	1419	2399	4084	111,961			
Person-years	14,022	27,155	46,281	1,260,207			
Number of cases	186	259	403	12,747			
ASR (per 100,000)	1168	1034	1111	1096			
HR1	1.0 (Ref.)	0.91 (0.73, 1.13)	0.89 (0.74, 1.07)	0.93 (0.80, 1.07)	*1.00*	0.41	0.61
HR2	1.0 (Ref.)	0.92 (0.72, 1.16)	0.91 (0.76, 1.1)	0.97 (0.83, 1.13)	*0.99*	0.37	0.54
HR3	1.0 (Ref.)	0.91 (0.72, 1.15)	0.99 (0.80, 1.22)	1.04 (0.88, 1.24)	*0.84*	0.81	0.70
Fruits							
Number of subjects	21,334	20,521	25,347	53,251			
Person-years	235,870	238,040	291,188	588,616			
Number of cases	2433	2170	2735	6325			
ASR (per 100,000)	1139	1106	1086	1076			
HR1	1.0 (Ref.)	0.99 (0.90, 1.08)	0.95 (0.89, 1.01)	0.94 (0.88, 0.997)	*0.07*	0.17	0.45
HR2	1.0 (Ref.)	1.01 (0.92, 1.1)	0.99 (0.93, 1.05)	1.02 (0.96, 1.08)	*1.00*	0.21	0.37
HR3	1.0 (Ref.)	1.02 (0.92, 1.13)	1.00 (0.92, 1.07)	1.03 (0.95, 1.12)	*1.00*	0.07	0.28
Fruits, excluding juice							
Number of subjects	24,401	19,825	17,380	30,938			
Person-years	279,605	245,514	214,934	354,828			
Number of cases	2916	2204	2056	3886			
ASR (per 100,000)	1188	1176	1158	1087			
HR1	1.0 (Ref.)	0.94 (0.89, 1.00)	0.92 (0.86, 0.99)	0.89 (0.85, 0.94)	*<0.01*	0.45	0.48
HR2	1.0 (Ref.)	0.97 (0.91, 1.03)	0.98 (0.92, 1.04)	0.98 (0.93, 1.03)	*0.80*	0.80	0.92
HR3	1.0 (Ref.)	0.96 (0.89, 1.03)	0.97 (0.91, 1.04)	1.00 (0.87, 1.15)	*0.77*	<0.01	0.74
Vegetables							
Number of subjects	2641	3942	6530	107,041			
Person-years	27,695	44,538	73,935	1,204,774			
Number of cases	335	400	644	12,254			
ASR (per 100,000)	1155	1049	1037	1099			
HR1	1.0 (Ref.)	0.92 (0.79, 1.06)	0.92 (0.80, 1.05)	0.96 (0.86, 1.07)	*1.00*	0.64	0.99
HR2	1.0 (Ref.)	0.93 (0.80, 1.08)	0.94 (0.82, 1.07)	0.99 (0.89, 1.11)	*0.95*	0.73	0.97
HR3	1.0 (Ref.)	0.96 (0.81, 1.14)	0.98 (0.84, 1.14)	1.04 (0.91, 1.18)	*0.84*	0.94	0.77
Vegetables, excluding pickles							
Number of subjects	6318	5797	15,681	92,736			
Person-years	68,320	65,009	180,846	1,040,467			
Number of cases	756	587	1618	10,717			
ASR (per 100,000)	1160	1068	1050	1099			
HR1	1.0 (Ref.)	0.91 (0.81, 1.01)	0.95 (0.87, 1.05)	0.96 (0.89, 1.04)	*1.00*	0.93	0.99
HR2	1.0 (Ref.)	0.91 (0.82, 1.01)	0.97 (0.89, 1.07)	0.99 (0.92, 1.07)	*0.97*	0.97	0.98
HR3	1.0 (Ref.)	0.92 (0.79, 1.07)	0.99 (0.90, 1.10)	1.00 (0.91, 1.09)	*0.91*	0.79	0.86
Green and yellow vegetables							
Number of subjects	12,418	15,054	27,422	65,748			
Person-years	132,772	162,075	306,687	754,274			
Number of cases	1396	1509	2920	7869			
ASR (per 100,000)	1131	1057	1088	1097			
HR1	1.0 (Ref.)	0.95 (0.82, 1.10)	0.96 (0.89, 1.04)	0.94 (0.86, 1.03)	*0.69*	0.07	0.49
HR2	1.0 (Ref.)	0.96 (0.82, 1.12)	0.99 (0.92, 1.05)	0.99 (0.91, 1.08)	*1.00*	0.13	0.83
HR3	1.0 (Ref.)	0.97 (0.81, 1.15)	0.99 (0.91, 1.07)	1.01 (0.91, 1.11)	*1.00*	0.08	0.40

ASR, age-standardized rate; CI, confidence interval; HR, hazard ratio.
HR1 was adjusted for age (continuous), area (for JPHC-I, JPHC-II only). HR2 and 3: further adjusted for total energy intake (quintile), smoking status (never, past, <19, 19–39, or ≥40 cigarettes/day), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). HR3 excluded diagnosed or deceased cases of any cancers during the first 3 years of follow-up. Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.

Three very large-scale (including over 100,000 subjects) prospective cohort studies reported to date have found a very small inverse or no association between vegetables and overall cancers[6,9,10] and no association for fruit, with consistency among the studies.[9] The pooled analysis of the Health Professionals' Follow-up Study and Nurses' Health Study in 109,635 subjects (9261 cancer cases) reported relative risks for the incidence of overall cancer of 1.01 (95% CI, 0.95–1.06) for fruit and 0.99 (95% CI, 0.95–1.04) for vegetables by continuous measure for increments of three servings.[6] The European Prospective Investigation Into Cancer and Nutrition Study in 478,478 subjects (30,604 cancer cases) reported a very small inverse association for vegetables only (HR by increments of 100 g/day, 0.98; 95% CI, 0.97–0.99) but not for fruit (HR 0.99; 95% CI, 0.98–1.00).[10] Finally, the National Institutes of Health-American Association of Retired Persons Diet and Health Study reported relative risks for the highest quintiles of fruit or vegetables of 0.98 (95% CI, 0.95–1.02; trend p = 0.17) and 0.94 (95% CI, 0.91–0.97; trend p < 0.01), respectively, among 288,109 (35,071 incident cases) men, and 0.99 (95% CI, 0.94–1.05; trend p = 0.06) and 1.04 (95% CI, 0.98–1.09; trend p = 0.08), respectively, among 195,229 (15,792 cases) women.[9] However, all of these studies were conducted in Western populations (in the United States[6,9] and Europe[10]), and no such large-scale data from Asian populations have been reported to date.

Table 5-2
Pooled analysis of total cancer incidence according to frequency of fruit and vegetable intake among 133,350 Japanese women, 1990–2006.

	Almost never	1-2/week	3-4/week	Almost daily	p for trend	p for heterogeneity	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		for the highest category	For trend
Total fruit and vegetables							
Number of subjects	1035	1347	1944	127,745			
Person-years	10,492	15,843	22,634	1,498,738			
Number of cases	79	79	134	8324			
ASR (per 100,000)	676	459	645	585			
HR1	1.0 (Ref.)	0.69 (0.5, 0.97)	0.97 (0.66, 1.44)	0.87 (0.67, 1.14)	*1.00*	0.28	0.69
HR2	1.0 (Ref.)	0.69 (0.49, 0.97)	0.96 (0.66, 1.4)	0.88 (0.67, 1.15)	*1.00*	0.27	0.55
HR3	1.0 (Ref.)	0.67 (0.45, 1)	0.97 (0.6, 1.57)	0.90 (0.64, 1.27)	*1.00*	0.20	0.20
Fruits							
Number of subjects	12,464	13,402	22,478	84,523			
Person-years	143,440	162,964	271,785	978,385			
Number of cases	871	880	1354	5568			
ASR (per 100,000)	610	599	548	588			
HR1	1.0 (Ref.)	0.94 (0.85, 1.04)	0.89 (0.82, 0.98)	0.93 (0.87, 1.00)	*0.94*	0.93	0.88
HR2	1.0 (Ref.)	0.95 (0.86, 1.05)	0.90 (0.82, 0.99)	0.95 (0.88, 1.02)	*1.00*	0.93	0.74
HR3	1.0 (Ref.)	0.92 (0.82, 1.03)	0.90 (0.81, 1.00)	0.95 (0.87, 1.03)	*1.00*	1.00	0.93
Fruits, excluding juice							
Number of subjects	14,619	12,474	17,730	56,108			
Person-years	175,283	160,159	230,565	680,397			
Number of cases	1000	851	1168	3791			
ASR (per 100,000)	596	630	580	584			
HR1	1.0 (Ref.)	0.99 (0.90, 1.10)	0.93 (0.83, 1.04)	0.96 (0.89, 1.03)	*0.77*	0.99	0.98
HR2	1.0 (Ref.)	1.00 (0.90, 1.10)	0.94 (0.84, 1.06)	0.97 (0.91, 1.05)	*0.97*	0.97	0.92
HR3	1.0 (Ref.)	0.97 (0.87, 1.08)	0.95 (0.83, 1.08)	0.97 (0.89, 1.05)	*0.99*	1.00	0.89
Vegetables							
Number of subjects	1874	2305	4164	123,992			
Person-years	20,199	27,103	49,354	1,454,268			
Number of cases	138	137	296	8068			
ASR (per 100,000)	598	577	646	584			
HR1	1.0 (Ref.)	0.84 (0.66, 1.07)	1.09 (0.77, 1.56)	0.91 (0.73, 1.15)	*0.98*	0.21	0.73
HR2	1.0 (Ref.)	0.84 (0.66, 1.07)	1.09 (0.77, 1.54)	0.92 (0.72, 1.18)	*1.00*	0.17	0.51
HR3	1.0 (Ref.)	0.92 (0.68, 1.23)	1.08 (0.8, 1.46)	1.01 (0.74, 1.37)	*1.00*	0.14	0.29
Vegetables, excluding pickles							
Number of subjects	3953	3416	11,615	113,897			
Person-years	44,361	39,777	138,591	1,334,133			
Number of cases	281	240	763	7397			
ASR (per 100,000)	591	653	595	581			
HR1	1.0 (Ref.)	1.08 (0.76, 1.54)	0.94 (0.74, 1.2)	0.91 (0.75, 1.12)	*0.59*	0.10	0.69
HR2	1.0 (Ref.)	1.09 (0.77, 1.53)	0.94 (0.73, 1.21)	0.92 (0.74, 1.15)	*0.88*	0.07	0.61
HR3	1.0 (Ref.)	1.15 (0.79, 1.68)	0.99 (0.78, 1.26)	0.94 (0.73, 1.22)	*0.90*	0.05	0.33
Green and yellow vegetables							
Number of subjects	7217	10,283	24,528	91,010			
Person-years	78,742	112,495	278,824	1,088,495			
Number of cases	503	644	1556	5988			
ASR (per 100,000)	606	570	596	581			
HR1	1.0 (Ref.)	0.93 (0.82, 1.05)	0.96 (0.87, 1.07)	0.93 (0.85, 1.02)	*0.64*	0.63	0.49
HR2	1.0 (Ref.)	0.93 (0.80, 1.07)	0.97 (0.88, 1.08)	0.95 (0.86, 1.04)	*0.94*	0.50	0.58
HR3	1.0 (Ref.)	0.90 (0.75, 1.08)	0.96 (0.85, 1.08)	0.94 (0.84, 1.04)	*0.94*	0.46	0.52

ASR, age-standardized rate; CI, confidence interval; HR, hazard ratio.
HR1 was adjusted for age (continuous), area (for JPHC-I, JPHC-II only). HR2 and 3: further adjusted for total energy intake (quintile), smoking status (never, past, or current), alcohol consumption (non, occasional, <23, 23–45, or ≥46 g ethanol/day), body mass index in kg/m^2 (14–18.9, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, or 30–40 kg/m^2), history of diabetes mellitus (yes or no), and screening examination (yes or no; any kind of the following cancer screening for JPHC-I: chest X-ray, sputum test, photofluorography, gastrointestinal endoscopy, fecal occult blood test, barium enema, or colonoscopy; any kind of screening examination for JPHC-II; and chest X-ray, gastric cancer examination, Pap smear, mammography, or complete medical checkup for MIYAGI and OHSAKI). HR3 excluded diagnosed or deceased cases of any cancers during the first 3 years of follow-up. Linear trends across quintiles of fruit and vegetable intake were tested using 0 to 4 for each quintile as an ordinal variable.

Among studies in Asia reported to date, a relatively small-scale male cohort study (14,198 subject) in Korea reported an inverse association between vegetable intake and total cancer incidence (HR for ≥300 g/day vs, <50 g/day of vegetables: 0.72; 95% CI, 0.58–0.90; trend p = 0.02) but not for fruit (HR 1.04; 95% CI, 0.87–1.25; trend p = 0.56).[25] Also, a large-scale (134,796 subject) cohort study in China (Shanghai Women's and Men's Health Study), which treated mortality as the primary outcome, reported no association of fruit and vegetable intakes with cancer but an inverse association with CVD: corresponding HRs for the highest versus lowest quintile of intake were 0.96 (95% CI, 0.83–1.10) and 1.05 (95% CI, 0.90–1.21), respectively, for cancer (trend p = 0.25 and 0.58, respectively) versus 0.72 (95% CI, 0.59–0.87) and 0.74 (95% CI, 0.57–0.96), respectively, for CVD (trend p = 0.02 for both).[8] A previous Japanese study (the JPHC Study, with 77,891 subjects) reported that higher fruit intake was significantly associated with a lower risk of CVD incidence (HR for the highest vs. lowest quartile of intake: 0.81; 95% CI, 0.67–0.97; trend p = 0.01), although neither fruit nor vegetable intakes were associated with decreased risk of overall cancer incidence, with corresponding hazard ratios of 1.02 (95% CI, 0.90–1.14; trend p = 0.95) for fruit and 0.94 (95% CI, 0.84–1.05; trend p = 0.16) for vegetables.[7]

In the present study, adjustment for a common set of variables, such as smoking status, would bias the associations toward an increased risk. In the age- and area-adjusted HRs for fruit and vegetables, for example, our finding of an inverse and no association changed to no and a positive association, respectively, after adjustment for smoking status. A lower prevalence of ever smokers or heavy drinkers with higher fruit and vegetable consumption in the present cohort[7,16,26] would result in an increased risk after adjustment for these confounding factors. These results were notable among men, who had a higher prevalence of smoking than women. An association with vegetable intake was not seen when the multivariable-adjusted analysis was confined to never-smokers, but a marginally increased risk was seen when it was confined to smokers. In a similar pooled analysis of Japanese cohort studies, Wakai et al.[27] also reported a positive association between vegetable consumption and lung cancer incidence in the multivariate-adjusted analysis only (especially among ever smokers). However, in contrast to these results, no association with either fruit or vegetable intakes was shown when the analysis treated smoking-related cancers as the outcome of interest. These findings suggest substantial residual confounding by tobacco smoking.

The variation in fruit and vegetable consumption among subjects in this study is likely to be sufficiently large: cut-offs of the fourth and fifth quintiles of vegetable consumption were 2- to 3-fold higher than those for the first and second quintile in each cohort.[24] This is similar to previous studies that found very small inverse associations between vegetable intake and overall cancer (2.5- and 3-fold difference between these cut-offs for vegetables).[9,10] Also, a similar previous pooled analysis in Japan showed an inverse association between vegetable (but not fruit) intake and distal gastric cancer.[24] Further, fruit consumption did not show any inverse association in multivariate analysis, despite having consistently larger variation than vegetable intakes in the present and these previous studies (2- to 4-fold for vegetables, 3.2- to 6.5 fold for fruit).[6,9,10] These facts argue against the possibility that the observed absence of any inverse association with cancer incidence is attributable to insufficient variation in fruit and vegetable consumption.

Our study has several potential limitations. First, the validity of the FFQ for fruit and vegetable intake was moderate at best ($r = 0.3$ to 0.7).[20,21] Measurement error in the FFQ would have biased the association of fruit or vegetable intakes with overall cancer toward the null, and the observed associations would have thereby underestimated the true magnitude of a small protective association. Second, the difference in true absolute intake among the cohorts cannot be calibrated. Although sub-analyses using frequency categories and a larger number of subjects and cancer cases (6 cohorts) than in the present did not differ from the present main analysis by quintiles of energy-adjusted intake, we cannot entirely rule out the possibility of misclassification among the cohort caused by the different number of items from the different FFQs. Third, we used and adjusted for a study-specific question on cancer screening examination (varieties and time span). Although detection bias resulting from health conscious behaviors, such as participation in cancer screening examination and higher fruit and vegetable consumption, likely accounted for the positive association on assessment using cancer incidence as outcomes, our results did not substantially change before and after adjustment for cancer screening in the present study. Although we have adjusted for possible confounding variables in common categories as much as possible, the effects of residual confounding by unmeasured or unstandardized variables cannot be totally discarded.

Although the impact for overall cancer prevention was undetectable, the results do not contradict the possibly small but protective effect of fruit and vegetable intakes for site-specific cancers, such as stomach cancer,[1,24] lung cancer,[27] or breast cancer by hormone receptor status.[28,29] It is possible that the aggregation of cancer sites in the analysis might dilute the impact of association. Therefore, in accordance with the biological plausibility, the recommendation that "higher consumption of several plant foods probably protects against cancers of various sites" may still be applicable in Japan.[1]

In conclusion, the results of this pooled analysis of large-scale population-based prospective cohort studies in Japan do not provide evidence for inverse associations of fruit or vegetable consumption with risk of overall cancer incidence.

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Conflicts of interest

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