Table 1. Characteristics of the 7 cohort studies included in a pooled analysis of body mass index and risk of all-cause and major-cause mortality

Study	Population	Age (years) at baseline survey	Year(s) of baseline survey	Population size	Rate of response (%) to baseline questionnaire	Method of follow-up	The present pooled analysis						
							Age (years)	Last follow-up time	Mean duration of follow-up (years)	Size of cohort		Number of total deaths	
										Men	Women	Men	Women
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990	61 595	82%	Death certificates	40–59	2005	14.2	23 156	26 104	2392	1194
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–1994	78 825	80%	Death certificates	40–69	2005	11.3	29 015	32 484	3672	1802
JACC	Residents of 45 areas throughout Japan	40–79	1988–1990	110 792	83%	Death certificates	40–79	2006	14.7	41 639	57 147	10 575	7351
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47 605	92%	Death certificates	40–64	2004 (all causes), 2001 (cause-specific)	13.5 10.3	20 832	22 616	2097 1409	1041 699
OHSAKI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	52 029	95%	Death certificates	40–79	2006	10.0	21 008	22 886	3675	2015
3-pref AICHI	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985	33 529	90%	Death certificates	40–103	2000	11.7	13 841	15 296	2516	1866
TAKAYAMA	Japanese residents of Takayama, Gifu, Japan	≥35	1992	31 552	85%	Death certificates	35–101	1999	6.9	12 601	14 797	1017	767
Total										162 092	191 330	25 944	16 036

Abbreviations: JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; OHSAKI, Ohsaki National Health Insurance Cohort Study; 3-pref AICHI, The Three Prefecture Study - Aichi portion; TAKAYAMA, Takayama Study.

Table 2. Pooled analysis of BMI and mortality (Men)

	14–<19 HR (95% CI)	19–<21 HR (95% CI)	21–<23 HR (95% CI)	23–<25 HR (95% CI)	25–<27 HR (95% CI)	27–<30 HR (95% CI)	30–<40 HR (95% CI)	Heterogeneity I squared (%) and *P* for the lowest category	highest category
All Causes									
Number of subjects (*n* = 162 092)	9933	28 571	44 035	42 354	23 238	11 448	2513		
Person-years 1 967 103	108 482	342 361	538 369	522 805	287 923	141 921	25 243		
Number of deaths (*n* = 25 944)	3162	5717	7022	5519	2728	1420	376		
Crude rate (per 100 000)	2914.77	1669.88	1304.31	1055.65	947.48	1000.56	1489.53		
Age-standardized rate (per 100 000)	2009.45	1483.13	1283.1	1144.92	1086.56	1205.09	1495.49		
Age- and area-adjusted (HR1)[a]	**1.83 (1.64–2.05)**	**1.30 (1.24–1.37)**	**1.12 (1.05–1.19)**	1.00 (Reference)	0.95 (0.91–0.996)	1.09 (0.97–1.21)	**1.42 (1.22–1.65)**	80.6% (*P* < 0.0001)	46.6% (*P* = 0.081)
Multivariate-adjusted (HR2)[b]	**1.78 (1.60–1.98)**	**1.27 (1.22–1.33)**	**1.11 (1.04–1.18)**	1.00 (Reference)	0.94 (0.90–0.99)	1.07 (0.97–1.17)	**1.36 (1.19–1.55)**	77.1% (*P* < 0.0001)	32.3% (*P* = 0.181)
Multivariate-adjusted, excl. early death (HR3)[c]	**1.64 (1.50–1.79)**	**1.24 (1.19–1.29)**	**1.10 (1.03–1.17)**	1.00 (Reference)	0.96 (0.91–1.01)	1.09 (0.97–1.22)	**1.35 (1.11–1.65)**	52.8% (*P* = 0.048)	59.4% (*P* = 0.022)
Cancer									
Number of subjects (*n* = 162 092)	9933	28 571	44 035	42 354	23 238	11 448	2513		
Person-years 1 909 493	106 697	333 333	521 589	504 796	277 359	136 168	29 551		
Number of deaths (*n* = 10 115)	1022	2252	2873	2269	1056	516	127		
Crude rate (per 100 000)	957.85	675.60	550.82	449.49	380.73	378.94	429.76		
Age-standardized rate (per 100 000)	730.77	614.48	541.64	479.33	426.71	437.22	526.94		
Age- and area-adjusted (HR1)[a]	**1.52 (1.31–1.77)**	**1.29 (1.19–1.40)**	**1.13 (1.04–1.22)**	1.00 (Reference)	0.90 (0.83–0.96)	0.97 (0.85–1.10)	1.18 (0.95–1.47)	68.9% (*P* = 0.004)	27.8% (*P* = 0.226)
Multivariate-adjusted (HR2)[b]	**1.44 (1.24–1.67)**	**1.23 (1.13–1.34)**	**1.10 (1.02–1.19)**	1.00 (Reference)	0.90 (0.84–0.97)	0.98 (0.86–1.12)	1.20 (0.97–1.50)	67.7% (*P* = 0.005)	27.2% (*P* = 0.231)
Multivariate-adjusted, excl. early death (HR3)[c]	**1.27 (1.12–1.43)**	**1.17 (1.09–1.26)**	1.08 (0.997–1.18)	1.00 (Reference)	0.95 (0.87–1.03)	1.02 (0.86–1.22)	**1.29 (1.05–1.58)**	27.6% (*P* = 0.218)	0.0% (*P* = 0.460)
Heart Disease									
Number of subjects (*n* = 162 092)	9933	28 571	44 035	42 354	23 238	11 448	2513		
Person-years 1 909 493	106 697	333 333	521 589	504 796	277 359	136 168	29 551		
Number of deaths (*n* = 3378)	383	671	887	725	411	237	64		
Crude rate (per 100 000)	358.96	201.30	170.06	143.62	148.18	174.05	216.57		
Age-standardized rate (per 100 000)	231.78	176.19	167.33	157.75	170.83	215.61	276.87		
Age- and area-adjusted (HR1)[a]	**1.47 (1.24–1.74)**	**1.11 (1.00–1.24)**	1.05 (0.95–1.16)	1.00 (Reference)	1.05 (0.86–1.29)	1.37 (0.998–1.87)	**1.85 (1.43–2.39)**	27.7% (*P* = 0.217)	0.0% (*P* = 0.711)
Multivariate-adjusted (HR2)[b]	**1.45 (1.21–1.74)**	**1.11 (1.00–1.24)**	1.05 (0.95–1.16)	1.00 (Reference)	1.03 (0.84–1.25)	1.28 (0.95–1.74)	**1.71 (1.32–2.22)**	34.5% (*P* = 0.164)	0.0% (*P* = 0.765)
Multivariate-adjusted, excl. early death (HR3)[c]	**1.28 (1.04–1.59)**	1.10 (0.96–1.24)	1.01 (0.89–1.15)	1.00 (Reference)	1.04 (0.83–1.31)	1.17 (0.83–1.65)	**1.72 (1.22–2.43)**	25.7% (*P* = 0.232)	13.4% (*P* = 0.328)

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	14–<19 HR (95% CI)	19–<21 HR (95% CI)	21–<23 HR (95% CI)	23–<25 HR (95% CI)	25–<27 HR (95% CI)	27–<30 HR (95% CI)	30–<40 HR (95% CI)	Heterogeneity I squared (%) and *P* for the lowest category	Heterogeneity I squared (%) and *P* for the highest category
Cerebrovascular Disease									
Number of subjects (*n* = 162 092)	9933	28 571	44 035	42 354	23 238	11 448	2513		
Person-years 1 909 493	106 697	333 333	521 589	504 796	277 359	136 168	29 551		
Number of deaths (*n* = 2820)	332	625	737	605	309	162	50		
Crude rate (per 100 000)	311.16	187.50	141.30	119.85	111.41	118.97	169.20		
Age-standardized rate (per 100 000)	201.17	161.94	138.77	133.33	132.93	153.72	218.73		
Age- and area-adjusted (HR1)[a]	**1.43 (1.20–1.71)**	**1.21 (1.06–1.39)**	1.03 (0.92–1.15)	1.00 (Reference)	1.01 (0.88–1.16)	1.19 (0.996–1.41)	**1.81 (1.35–2.42)**	22.5% (*P* = 0.257)	0.0% (*P* = 0.511)
Multivariate-adjusted (HR2)[b]	**1.53 (1.26–1.85)**	**1.28 (1.10–1.49)**	1.05 (0.94–1.17)	1.00 (Reference)	0.97 (0.84–1.11)	1.10 (0.92–1.31)	**1.64 (1.23–2.20)**	29.4% (*P* = 0.204)	0.0% (*P* = 0.671)
Multivariate-adjusted, excl. early death (HR3)[c]	**1.52 (1.23–1.89)**	**1.21 (1.06–1.38)**	1.02 (0.89–1.15)	1.00 (Reference)	0.95 (0.75–1.20)	1.11 (0.91–1.36)	**1.54 (1.06–2.24)**	22.3% (*P* = 0.259)	4.9% (*P* = 0.391)
Other Causes									
Number of subjects (*n* = 162 092)	9933	28 571	44 035	42 354	23 238	11 448	2513		
Person-years 1 909 493	106 697	333 333	521 589	504 796	277 359	136 168	29 551		
Number of deaths (*n* = 8950)	1388	2047	2347	1751	861	448	108		
Crude rate (per 100 000)	1300.87	614.10	449.97	346.87	310.43	329.00	365.46		
Age-standardized rate (per 100 000)	853.68	538.23	443.38	380.67	361.97	362.07	370.2		
Age- and area-adjusted (HR1)[a]	**2.49 (2.14–2.90)**	**1.43 (1.33–1.55)**	**1.18 (1.08–1.29)**	1.00 (Reference)	0.94 (0.85–1.04)	1.08 (0.97–1.20)	**1.35 (1.00–1.83)**	70.9% (*P* = 0.002)	53.0% (*P* = 0.047)
Multivariate-adjusted (HR2)[b]	**2.15 (2.10–2.79)**	**1.42 (1.32–1.54)**	**1.17 (1.07–1.28)**	1.00 (Reference)	0.93 (0.84–1.03)	1.05 (0.95–1.17)	1.29 (0.95–1.74)	65.6% (*P* = 0.008)	52.4% (*P* = 0.050)
Multivariate-adjusted, excl. early death (HR3)[c]	**2.31 (1.99–2.69)**	**1.43 (1.30–1.57)**	**1.16 (1.08–1.25)**	1.00 (Reference)	0.93 (0.84–1.02)	1.10 (0.98–1.24)	1.22 (0.85–1.76)	53.0% (*P* = 0.047)	51.2% (*P* = 0.056)

[a]Adjusted for age (years, continuous) and area (for JPHC-I, JPHC-II, and JACC only) (HR1).
[b]Further adjusted for cigarette smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day or ≥20 cigarettes/day), alcohol drinking (nondrinkers [never- or ex-drinker], occasional drinkers (less than once per week), regular drinkers (almost daily for OHSAKI and 3-pref AICHI; ≥5 days/week for JPHCI, JPHCII, and JACC; ≥5 times/week for MIYAGI; and ≥4–6 days/week for TAKAYAMA), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (less than almost daily, almost daily) (HR2).
[c]Excluding deaths within 5 years (HR3). Bold text: $P < 0.05$.

category improved, which suggests that different conditions of early death across studies were the main reason for the heterogeneity seen among individuals with a lower BMI. Due to the relatively small number of subjects in the highest BMI category, the same process increased the I^2 in some outcomes for that category.

In women, a reverse J-shaped association was also observed for all-cause and other-cause mortality, but not for cancer (Table 3). For all-cause mortality, after fully adjusting for potential confounding factors (HR2) and using a BMI range of 23 to 25 kg/m^2 as the basis for comparison, the HRs for BMI ranges 14 to 19, 19 to 21, 27 to 30, and 30 to 40 kg/m^2 were estimated as 1.61, 1.17, 1.08, and 1.37, respectively. For cancer, a statistically significant increased risk was observed only for obesity, and there was no evidence of increased risk at any lower BMI range. After fully adjusting for confounding factors (HR2) and comparing with BMI range 23 to 25 kg/m^2, the HR for BMI range 30 to 40 kg/m^2 was 1.25. As with men, a U-shaped or J-shaped association was observed for heart disease and cerebrovascular disease in women. The risk elevation at lower and higher BMIs was more apparent for heart disease: the HRs for BMI ranges 14 to 19 and 30 to 40 kg/m^2 were 1.77 and 1.79 for heart disease and 1.44 and 1.30 for cerebrovascular disease, respectively. For all-cause and other-cause mortality, exclusion of early deaths slightly attenuated the results, but they remained significant. Furthermore, heterogeneity seen in the lowest category became nonsignificant.

When men were stratified by smoking status, the association between mortality and low BMI was generally more pronounced among current smokers than among never smokers (Table 4). This modification effect was most pronounced in cancer mortality, for which the observed risk elevation in the low BMI range disappeared among never smokers but remained among current smokers. The HRs for BMI ranges 14 to 19, 19 to 21, and 21 to 23 kg/m^2 were 1.05, 0.96, and 0.95, respectively, for never smokers and 1.49, 1.23, and 1.11 for current smokers. The heterogeneity in outcomes may be due in part to the relatively small sample size in the stratified analysis, and the results may not affect the above findings.

The data suggest that approximately 0.9% and 1.5% of total deaths were attributable to a high BMI ($\geq$27 kg/m^2) in men and women, respectively, as were 0.2% and 1.0% of cancer deaths, 2.8% and 2.7% of heart disease deaths, and 1.5% and 1.9% of cerebrovascular deaths.

DISCUSSION

In this pooled analysis of more than 350 000 Japanese, an elevated risk of all-cause mortality for both high and low BMI levels was observed in both sexes. This association remained after excluding early deaths during follow-up and after restricting the analysis to never smokers (in men). The results conform with most previous cohort studies in Japan, which showed a U-shaped[7,9] or reverse J-shaped association.[10] Other studies showed no obvious increase in risk due to obesity in men[5,8] or women,[6] due to the older age of the subjects or the small number of subjects in the respective categories. All-cause mortality was lowest at a BMI range of 23 to 27 kg/m^2 in men and 21 to 27 kg/m^2 in women. Above this range, a significant increase in risk was observed only at a BMI range of 30 to 40 kg/m^2 in men and 27 kg/m^2 or higher in women. Men with a BMI of 27 to 30 kg/m^2 had a slightly elevated risk, which was not statistically significant. Four of 7 individual studies included in the pooled analysis showed an elevated risk, and among these, 3 found a statistically significant association; the HR range was 1.13 to 1.36. Therefore, we believe that a BMI greater than 27 kg/m^2 should be defined as a high-risk group for overall mortality in both men and women and that it is not necessary to set a higher or lower cut-off point in this population.

Cancer accounted for 37% (39% in men and 35% in women) of overall deaths. The association of BMI with cancer was similar to that observed for BMI and all-cause mortality in men. It has been observed in many studies that low BMI is associated with increased risk of cancer.[21,29,30] As the effect-measure modification by cigarette smoking suggests, the risk elevation with low BMI in men is probably mostly due to smoking-related cancers (eg, cancers of the lung and esophagus, among others). In this population, most women were nonsmokers and thus no risk elevation was observed among women with a low BMI. Evidence of a positive association between high BMI and cancer risk comes mainly from Western populations, as shown in the Cancer Prevention Study-II[31–34] and the Million Women Study.[35,36] Among previous cohort studies conducted in Japan, only 1 showed a statistically significant positive association between high BMI and cancer incidence in women, which was attributed to cancers of the breast (postmenopausal), endometrium, gallbladder, and colorectum.[37] That study and another study[21] suggested that men were also at increased risk, and another study found that both men and women were at increased risk.[30] However, none of these findings were statistically significant. This may be due to the smaller proportion of overweight people in Japan as compared with Western countries. By pooling data, the present study revealed that obesity does increase the risk of mortality from cancer, although the contribution to the overall cancer burden was small.

For heart disease and cerebrovascular disease, a U- or J-shaped association was observed among men and women. Many epidemiologic studies have shown that obesity is a significant risk factor for developing heart disease and cerebrovascular disease. A continuous positive association was observed between BMI and the incidences of ischemic heart disease and stroke[38] and mortality[29] in collaborative analyses of prospective studies involving 310 000 participants from the Asia-Pacific region and 900 000 participants mainly from Western Europe and North America, respectively. In

Table 3. Pooled analysis of BMI and mortality (Women)

	14–<19 HR (95% CI)	19–<21 HR (95% CI)	21–<23 HR (95% CI)	23–<25 HR (95% CI)	25–<27 HR (95% CI)	27–<30 HR (95% CI)	30–<40 HR (95% CI)	Heterogeneity I squared (%) and *P* for the lowest category	Heterogeneity I squared (%) and *P* for the highest category
All Causes									
Number of subjects (*n* = 191 303)	15 027	34 289	50 450	44 316	26 341	16 066	4814		
Person-years 2 432 005	176 627	426 608	644 023	572 803	342 343	207 994	61 606		
Number of deaths (*n* = 16 036)	2302	2929	3702	3155	2081	1341	526		
Crude rate (per 100 000)	1303.32	686.58	574.82	550.80	607.87	644.73	853.81		
Age-standardized rate (per 100 000)	941.03	671.12	602.87	587.28	623.57	662.05	861.61		
Age- and area-adjusted (HR1)[a]	**1.57 (1.49–1.66)**	**1.15 (1.08–1.22)**	1.03 (0.97–1.09)	1.00 (Reference)	1.06 (0.997–1.13)	**1.15 (1.08–1.23)**	**1.51 (1.37–1.65)**	0.0% (*P* = 0.436)	0.0% (*P* = 0.739)
Multivariate-adjusted (HR2)[b]	**1.61 (1.53–1.71)**	**1.17 (1.11–1.23)**	1.03 (0.98–1.09)	1.00 (Reference)	1.04 (0.98–1.10)	**1.08 (1.02–1.16)**	**1.37 (1.24–1.50)**	0.0% (*P* = 0.728)	0.0% (*P* = 0.800)
Multivariate-adjusted, excl. early death (HR3)[c]	**1.55 (1.45–1.65)**	**1.17 (1.10–1.24)**	1.03 (0.98–1.09)	1.00 (Reference)	1.07 (0.95–1.21)	**1.10 (1.03–1.18)**	**1.34 (1.17–1.54)**	0.0% (*P* = 0.643)	50.5% (*P* = 0.059)
Cancer									
Number of subjects (*n* = 191 303)	15 027	34 289	50 450	44 316	26 341	16 066	4814		
Person-years 2 359 991	173 647	416 348	626 108	554 620	329 853	200 022	59 393		
Number of deaths (*n* = 5575)	554	970	1352	1244	789	491	175		
Crude rate (per 100 000)	319.04	232.98	215.94	224.30	239.20	245.47	294.65		
Age-standardized rate (per 100 000)	267.45	235.79	223.67	231.51	237.09	241.52	289.2		
Age- and area-adjusted (HR1)[a]	1.13 (0.95–1.35)	1.01 (0.92–1.10)	1.01 (0.90–1.13)	1.00 (Reference)	1.04 (0.95–1.13)	1.07 (0.96–1.19)	**1.30 (1.11–1.52)**	56.8% (*P* = 0.031)	0.0% (*P* = 0.909)
Multivariate-adjusted (HR2)[b]	1.12 (0.93–1.35)	1.00 (0.92–1.09)	1.00 (0.90–1.12)	1.00 (Reference)	1.03 (0.94–1.13)	1.05 (0.94–1.17)	**1.25 (1.07–1.47)**	59.1% (*P* = 0.023)	0.0% (*P* = 0.935)
Multivariate-adjusted, excl. early death (HR3)[c]	1.10 (0.92–1.31)	1.00 (0.91–1.11)	1.00 (0.88–1.13)	1.00 (Reference)	1.04 (0.93–1.15)	1.11 (0.98–1.25)	**1.28 (1.07–1.54)**	36.1% (*P* = 0.153)	0.0% (*P* = 0.988)
Heart Disease									
Number of subjects (*n* = 191 303)	15 027	34 289	50 450	44 316	26 341	16 066	4814		
Person-years 2 359 991	173 647	416 348	626 108	554 620	329 853	200 022	59 393		
Number of deaths (*n* = 2562)	385	429	548	423	300	381	96		
Crude rate (per 100 000)	221.71	103.04	87.52	76.27	90.95	190.48	161.64		
Age-standardized rate (per 100 000)	141.27	97.84	92.88	83.64	96.36	102.26	167.38		
Age- and area-adjusted (HR1)[a]	**1.62 (1.38–1.91)**	1.26 (0.98–1.62)	1.10 (0.97–1.25)	1.00 (Reference)	1.15 (0.99–1.33)	**1.26 (1.03–1.55)**	**2.10 (1.68–2.63)**	7.2% (*P* = 0.373)	0.0% (*P* = 0.759)
Multivariate-adjusted (HR2)[b]	**1.77 (1.45–2.15)**	**1.32 (1.02–1.70)**	1.11 (0.98–1.27)	1.00 (Reference)	1.11 (0.96–1.29)	1.15 (0.91–1.44)	**1.79 (1.43–2.24)**	23.8% (*P* = 0.247)	0.0% (*P* = 0.790)
Multivariate-adjusted, excl. early death (HR3)[c]	**1.56 (1.26–1.91)**	1.20 (0.98–1.48)	1.11 (0.96–1.28)	1.00 (Reference)	1.11 (0.93–1.31)	1.10 (0.81–1.50)	**1.88 (1.41–2.51)**	11.5% (*P* = 0.342)	9.7% (*P* = 0.355)

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		14–<19 HR (95% CI)	19–<21 HR (95% CI)	21–<23 HR (95% CI)	23–<25 HR (95% CI)	25–<27 HR (95% CI)	27–<30 HR (95% CI)	30–<40 HR (95% CI)	Heterogeneity I squared (%) and *P* for the lowest category	highest category
Cerebrovascular Disease										
Number of subjects	(*n* = 191 303)	15 027	34 289	50 450	44 316	26 341	16 066	4814		
Person-years	2 359 991	173 647	416 348	626 108	554 620	329 853	200 022	59 393		
Number of deaths	(*n* = 2251)	345	397	467	455	288	220	79		
Crude rate (per 100 000)		198.68	95.35	74.59	82.04	87.31	109.99	133.01		
Age-standardized rate (per 100 000)		137.28	92.44	78.75	89.87	91.29	117.61	134.98		
Age- and area-adjusted (HR1)[a]		**1.36 (1.06–1.74)**	1.02 (0.86–1.20)	0.87 (0.75–1.01)	1.00 (Reference)	0.99 (0.84–1.18)	**1.26 (1.01–1.58)**	**1.52 (1.20–1.94)**	50.0% (*P* = 0.062)	0.0% (*P* = 0.957)
Multivariate-adjusted (HR2)[b]		**1.44 (1.10–1.88)**	1.08 (0.91–1.28)	0.88 (0.76–1.03)	1.00 (Reference)	0.94 (0.79–1.13)	1.15 (0.93–1.41)	**1.30 (1.02–1.65)**	55.9% (*P* = 0.034)	0.0% (*P* = 0.981)
Multivariate-adjusted, excl. early death (HR3)[c]		1.32 (0.95–1.84)	1.07 (0.88–1.29)	0.88 (0.72–1.06)	1.00 (Reference)	0.95 (0.80–1.13)	1.14 (0.92–1.42)	**1.52 (1.16–1.99)**	50.3% (*P* = 0.060)	0.0% (*P* = 0.959)
Other Causes										
Number of subjects	(*n* = 191 303)	15 027	34 289	50 450	44 316	26 341	16 066	4814		
Person-years	2 359 991	173 647	416 348	626 108	554 620	329 853	200 022	59 393		
Number of deaths	(*n* = 5501)	1008	1089	1264	957	641	389	153		
Crude rate (per 100 000)		580.49	261.56	201.88	172.55	194.33	194.48	257.61		
Age-standardized rate (per 100 000)		410.16	251.81	23.32	187.3	202.61	201.71	264.17		
Age- and area-adjusted (HR1)[a]		**2.27 (1.91–2.69)**	**1.40 (1.19–1.64)**	**1.14 (1.00–1.29)**	1.00 (Reference)	1.10 (0.95–1.28)	1.12 (0.99–1.26)	**1.45 (1.22–1.73)**	61.6% (*P* = 0.016)	0.0% (*P* = 0.936)
Multivariate-adjusted (HR2)[b]		**2.32 (1.98–2.72)**	**1.44 (1.23–1.68)**	**1.15 (1.02–1.29)**	1.00 (Reference)	1.08 (0.94–1.24)	1.05 (0.94–1.19)	**1.31 (1.10–1.56)**	52.7% (*P* = 0.048)	0.0% (*P* = 0.894)
Multivariate-adjusted, excl. early death (HR3)[c]		**2.08 (1.83–2.36)**	**1.39 (1.19–1.63)**	1.14 (0.99–1.31)	1.00 (Reference)	1.05 (0.94–1.17)	1.08 (0.95–1.23)	**1.30 (1.07–1.57)**	13.3% (*P* = 0.328)	0.0% (*P* = 0.632)

[a]Adjusted for age (years, continuous) and area (for JPHC-I, JPHC-II, and JACC only) (HR1).
[b]Further adjusted for cigarette smoking (never smoker, past smoker, or current smoker), alcohol drinking (nondrinkers [never- or ex-drinker], occasional drinkers (less than once per week), regular drinkers (almost daily for OHSAKI and 3-pref AICHI; ≥5 days/week for JPHCI, JPHCII, and JACC; ≥5 times/week for MIYAGI; and ≥4–6 days/week for TAKAYAMA), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (less than almost daily, almost daily) (HR2).
[c]Excluding deaths within 5 years (HR3). Bold text: $P < 0.05$.

Table 4. Pooled analysis of BMI and mortality, stratified by smoking status (Men)

		14–<19 HR (95% CI)	19–<21 HR (95% CI)	21–<23 HR (95% CI)	23–<25 HR (95% CI)	25–<27 HR (95% CI)	27–<30 HR (95% CI)	30–<40 HR (95% CI)	Heterogeneity I squared (%) and *P* for the lowest category	Heterogeneity I squared (%) and *P* for the highest category
All Causes										
Never smokers, multivariate-adjusted[a]		**1.48 (1.25–1.77)**	1.16 (0.996–1.34)	0.98 (0.89–1.08)	1.00 (Reference)	0.91 (0.80–1.04)	1.05 (0.90–1.23)	1.42 (0.99–2.02)	32.9% (*P* = 0.177)	54.8% (*P* = 0.039)
Number of subjects	(*n* = 32 227)	1479	4527	8111	9060	5481	2899	670		
Person-years	405 361	17 107	55 839	102 982	114 276	69 710	37 126	8322		
Number of deaths	(*n* = 4422)	417	784	1110	1048	589	362	112		
Crude rate (per 100 000)		2437.61	1404.04	1077.86	917.08	844.93	975.07	1345.83		
Current smokers, multivariate-adjusted[a]		**1.68 (1.50–1.88)**	**1.22 (1.16–1.29)**	**1.09 (1.04–1.15)**	1.00 (Reference)	0.96 (0.90–1.03)	1.06 (0.98–1.16)	**1.40 (1.21–1.64)**	63.5% (*P* =0.012)	0.0% (*P* = 0.780)
Number of subjects	(*n* = 85 659)	5994	17 168	24 400	20 958	10 816	5186	1137		
Person-years	1 039 570	66 679	206 925	297 395	258 013	132 793	63 968	13 797		
Number of cases	(*n* = 14 191)	1828	3353	3960	2846	1363	662	179		
Crude rate (per 100 000)		2741.49	1620.39	1331.56	1103.05	1026.41	1034.89	1297.39		
Cancer										
Never smokers, multivariate-adjusted[a]		1.05 (0.81–1.36)	0.96 (0.81–1.15)	0.95 (0.82–1.11)	1.00 (Reference)	0.80 (0.61–1.04)	0.97 (0.77–1.21)	1.33 (0.91–1.94)	5.5% (*P* = 0.385)	0.0% (*P* = 0.874)
Number of subjects	(*n* = 32 227)	1479	4527	8111	9060	5481	2899	670		
Person-years	389 623	16 886	54 538	100 100	106 911	67 275	35 848	8066		
Number of deaths	(*n* = 1277)	90	211	340	345	162	99	30		
Crude rate (per 100 000)		532.99	386.88	339.66	322.70	240.80	276.16	371.92		
Current smokers, multivariate-adjusted[a]		**1.49 (1.23–1.81)**	**1.23 (1.12–1.36)**	**1.11 (1.02–1.20)**	1.00 (Reference)	0.97 (0.83–1.13)	0.98 (0.85–1.12)	1.30 (0.95–1.78)	68.5% (*P* = 0.004)	27.7% (*P* = 0.227)
Number of subjects	(*n* = 85 659)	5994	17 168	24 400	20 958	10 816	5186	1137		
Person-years	1 004 029	65 435	201 068	287 194	248 306	127 677	61 163	13 186		
Number of cases	(*n* = 5845)	664	1425	1701	1194	557	242	62		
Crude rate (per 100 000)		1014.74	708.72	592.28	480.86	436.26	395.67	470.19		
Heart Disease										
Never smokers, multivariate-adjusted[a]		1.36 (0.77–2.41)	1.11 (0.83–1.48)	0.93 (0.72–1.20)	1.00 (Reference)	1.09 (0.79–1.52)	1.35 (0.84–2.18)	**1.93 (1.01–3.67)**	41.4% (*P* = 0.129)	13.1% (*P* = 0.331)
Number of subjects	(*n* = 32 227)	1479	4527	8111	9060	5481	2899	670		
Person-years	389 623	16 886	54 538	100 100	106 911	67 275	35 848	8066		
Number of deaths	(*n* = 515)	46	89	124	120	78	45	13		
Crude rate (per 100 000)		272.42	163.19	123.88	112.24	115.94	125.53	161.16		
Current smokers, multivariate-adjusted[a]		**1.27 (1.03–1.56)**	0.98 (0.82–1.18)	0.99 (0.83–1.18)	1.00 (Reference)	1.10 (0.91–1.34)	1.25 (0.92–1.71)	**1.81 (1.18–2.77)**	14.4% (*P* = 0.320)	17.1% (*P* = 0.300)
Number of subjects	(*n* = 85 659)	5994	17 168	24 400	20 958	10 816	5186	1137		
Person-years	1 004 029	65 435	201 068	287 194	248 306	127 677	61 163	13 186		
Number of cases	(*n* = 1865)	211	380	514	391	222	115	32		
Crude rate (per 100 000)		322.45	188.99	178.97	157.47	173.88	188.02	242.68		

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		14–<19 HR (95% CI)	19–<21 HR (95% CI)	21–<23 HR (95% CI)	23–<25 HR (95% CI)	25–<27 HR (95% CI)	27–<30 HR (95% CI)	30–<40 HR (95% CI)	Heterogeneity I squared (%) and *P* for the lowest category	Heterogeneity I squared (%) and *P* for the highest category
Cerebrovascular Disease										
Never smokers, multivariate-adjusted[a]		1.32 (0.91–1.93)	1.32 (0.90–1.93)	0.99 (0.76–1.29)	1.00 (Reference)	1.10 (0.81–1.49)	1.23 (0.85–1.77)	**2.61 (1.35–5.04)**	0.0% (*P* = 0.851)	41.2% (*P* = 0.147)
Number of subjects	(*n* = 32 227)	1479	4527	8111	9060	5481	2899	670		
Person-years	389 623	16 886	54 538	100 100	106 911	67 275	35 848	8066		
Number of deaths	(*n* = 493)	43	92	119	109	73	42	15		
Crude rate (per 100 000)		254.65	168.69	118.88	101.95	108.51	117.16	185.96		
Current smokers, multivariate-adjusted[a]		**1.55 (1.28–1.87)**	1.20 (0.99–1.47)	1.02 (0.87–1.19)	1.00 (Reference)	0.98 (0.80–1.20)	1.10 (0.85–1.44)	1.41 (0.75–2.68)	0.0% (*P* = 0.611)	31.0% (*P* = 0.203)
Number of subjects	(*n* = 85 659)	5994	17 168	24 400	20 958	10 816	5186	1137		
Person-years	1 004 029	65 435	201 068	287 194	248 306	127 677	61 163	13 186		
Number of cases	(*n* = 1430)	193	341	381	288	141	70	16		
Crude rate (per 100 000)		294.95	169.59	132.66	115.99	110.43	114.45	121.34		
Other Causes										
Never smokers, multivariate-adjusted[a]		**1.99 (1.53–2.59)**	**1.28 (1.02–1.61)**	1.00 (0.79–1.28)	1.00 (Reference)	0.88 (0.72–1.09)	1.05 (0.81–1.37)	1.02 (0.65–1.60)	32.7% (*P* = 0.178)	0.0% (*P* = 0.554)
Number of subjects	(*n* = 32 227)	1479	4527	8111	9060	5481	2899	670		
Person-years	389 623	16 886	54 538	100 100	106 911	67 275	35 848	8066		
Number of deaths	(*n* = 1434)	187	288	357	317	163	101	21		
Crude rate (per 100 000)		1107.43	528.07	356.64	296.51	242.29	281.74	260.34		
Current smokers, multivariate-adjusted[a]		**2.24 (1.93–2.60)**	**1.35 (1.23–1.49)**	**1.16 (1.03–1.30)**	1.00 (Reference)	0.93 (0.80–1.08)	1.10 (0.94–1.28)	**1.51 (1.06–2.15)**	40.5% (*P* = 0.121)	33.8% (*P* = 0.170)
Number of subjects	(*n* = 85 659)	5994	17 168	24 400	20 958	10 816	5186	1137		
Person-years	1 004 029	65 435	201 068	287 194	248 306	127 677	61 163	13 186		
Number of cases	(*n* = 4627)	738	1120	1245	863	397	208	56		
Crude rate (per 100 000)		1127.83	557.03	433.51	347.55	310.94	340.08	424.69		

[a]Adjusted for age (years, continuous) and area (for JPHC-I, JPHC-II, and JACC only), cigarette smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day or ≥20 cigarettes/day), alcohol drinking (nondrinkers [never- or ex-drinker], occasional drinkers (less than once per week), regular drinkers (almost daily for OHSAKI and 3-pref AICHI; ≥5 days/week for JPHCI, JPHCII, and JACC; ≥5 times/week for MIYAGI; and ≥4–6 days/week for TAKAYAMA), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (less than almost daily, almost daily).

particular, dyslipidemia, diabetes mellitus, and hypertension are positively related to obesity.[39–41] These intermediate factors related to the disease may be largely accounted for by the elevated risk associated with a high BMI. However, the elevated risk was still significant even after controlling for histories of diabetes and hypertension (HR2). This suggests that another mechanism not explained by these factors might exist within the pathway. Funada et al and Cui et al reported an elevated risk of ischemic heart disease and hemorrhagic stroke not only among individuals with a high BMI, but also among those with a low BMI.[27,28] Several studies identified an association between low serum cholesterol level and hemorrhagic stroke.[42,43] Serum cholesterol level is positively correlated with BMI, which might explain the finding of elevated risk of hemorrhagic stroke among those with a low BMI. However, a definitive interpretation is not possible and further studies of the causal mechanisms linking low cholesterol and hemorrhagic stroke are needed.[43] In addition to cigarette smoking and preexisting disease, suggested mechanisms for the observed elevated risk of heart disease and cerebrovascular disease among individuals with low BMI include several cardiovascular abnormalities, such as reduced ventricular mass, valvular dysfunction, electrocardiographic changes, cardiac myofibril damage, and compromised immunity.[28]

As was the case for cause-specific mortality and all-cause mortality, both high and low BMI values were related to excess risk of other-cause mortality. Although the specific causes of death are unknown, some interpretations are possible. As mentioned above, a high BMI is associated with an increased risk of major chronic diseases and more people are likely to die from the complications of such diseases. Elevated risk was also observed among those with a low BMI, which suggests that people with a low BMI have less resistance to various diseases, including infectious, respiratory, or inflammatory diseases.

In Western countries, more attention is paid to overweight and obesity than to low BMI. In a collaborative analysis of data from 57 prospective studies of almost 900 000 adults, mostly in Western Europe and North America, a U-shaped association, similar to ours, was observed for overall mortality, with the lowest risk at a BMI of 22.5 to 25 kg/m^2 after controlling for early follow-up and smoking status.[29] However, the PAF was calculated for higher BMIs only, which seemed to be largely causal. Based on the relative risks and recent population BMI values, approximately 29% of vascular deaths and 8% of neoplastic deaths in late middle age in the United States were attributable to having a BMI greater than 25 kg/m^2. In the United Kingdom, the corresponding proportions were approximately 23% and 6%. In France, a working group of the International Agency for Research on Cancer reported that the PAF of all-cancer mortality due to obesity and overweight—calculated by summing the results of obesity-related cancers (ie, esophageal [adenocarcinoma], colorectal, kidney, corpus uteri, and breast [in postmenopausal women] cancers)—was 1.1% for men and 2.3% for women.[44]

The elevated risk of mortality among those within the low BMI range was most apparent for diseases of other causes, whose past history was not deleted. This indicates that reverse causation, namely, bias caused by preexisting illness and attendant weight loss, might partially explain the observed findings. To eliminate this possibility, we excluded deaths within 5 years, the method most frequently proposed to control for possible illness-related weight loss (IRWL).[23] We found that most RRs were attenuated and that heterogeneity across studies improved in the low BMI range. In the high BMI range, some RRs were attenuated while others were not, CIs increased, and heterogeneity was unchanged or increased. Using this indirect approach, individuals with IRWL are not necessarily excluded and those who are excluded do not necessarily have IRWL, which could introduce new sources of bias. Because no adequate method has been established to control for the effect of reverse causation, it is not possible to totally eliminate or clearly reveal the magnitude of the effect. However, the high prevalence of lean people in Japan indicates that a low BMI might be associated with mortality risk. In a pooled analysis of more than 1 million Asians, Zheng et al observed that underweight was associated with a substantially increased risk of death in all Asian populations.[4] They indicated that inadequate or incomplete control of confounding or reverse-causation bias might, in part, explain this increased risk. As Flegal et al indicate in their recent study, there is a need for studies with a more restricted focus and greater detail. Such studies might consider weight change or develop new methods of causal modeling.[45]

This study has several limitations. First, measures of abdominal obesity, such as waist circumference and waist-to-hip ratio, were not available. In the European Prospective Investigation on Cancer prospective study, both waist circumference and waist-to-hip ratio were strongly associated with risk of death, independent of BMI.[46] Therefore, the number of deaths attributable to all adiposity-related factors is probably greater than the present estimates. Second, the present BMI calculation was based on self-reported values. To minimize the effect of unreliable reporting, we excluded individuals reporting a BMI less than 14 or 40 kg/m^2 or higher. In the Takayama Study, the intraclass correlation coefficients between self-reported and measured height and weight in a subsample were 0.93 and 0.97 in both sexes, respectively.[18] In the JPHC study (combined JPHC-I and II, corresponding to 31.3% of the pooled dataset), self-reported BMI was slightly lower than measured BMI. In comparing self-reported height and weight with available data from health check-ups (11 274 men and 21 196 women), the Spearman correlation coefficient was 0.89 and 0.90 for men and women, respectively.[21] Similar underestimates of BMI, especially at higher weights, were also observed in a Western population.[47] It is uncertain whether the same was true for the other 4 studies; however, excess risk was observed only for a BMI of 30 kg/m^2 or higher across most of the end points, and the abovementioned effect is not likely to be large. Third, we used only single-point measurements of BMI as an exposure and did not capture weight change during the period. Accumulating evidence suggests that both weight gain and loss in adult life are associated with increased risk of mortality. We have previously observed that mortality from all causes and cancer is elevated by a weight loss of 5 kg or more after age 20 years[48] and during middle age,[49] whereas mortality from cardiovascular disease is elevated by a weight loss of 5 kg or more after age 20 in men[48] and weight gain during middle age in women.[49] Our combined findings indicate that maintaining an adequate weight in adulthood may be an important strategy for improving mortality in Japan. Limitations might also exist due to the process used for handling missing values. We chose to create an indicator term for missing data for each covariate, which might have led to biased estimates of the overall effect of the study exposure.[50]

The strength of this study is that it included most of the ongoing prospective studies in Japan, with overlapping birth generations and a similar survey time period. Therefore, pooling of these studies allows for a stable quantitative estimate of the impact of relative weight among Japanese. In addition, the categories of BMI and covariates used were identical among studies, which removes a potential source of heterogeneity that can occur in a meta-analysis of published literature.

In summary, the lowest risks of total mortality and mortality from major causes of diseases were observed at a BMI of 23 to 27 kg/m^2 for men and 21 to 27 kg/m^2 for women in middle-aged and elderly Japanese. Because there was no elevation of risk for a BMI of 21 to 23 in never-smoking men, we conclude that a BMI of 21 to 27 kg/m^2 is associated with the lowest mortality risk in both sexes.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Izumi Suenaga.

Conflicts of interest: The authors declare that they have no competing interests.

Funding: This study was supported by a Grant for the Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare of Japan.

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(5)693–708
doi:10.1093/jjco/hyr027
Advance Access Publication 19 March 2011

Lung Cancer Risk and Consumption of Vegetables and Fruit: An Evaluation Based on a Systematic Review of Epidemiological Evidence from Japan

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Received September 29, 2010; accepted February 9, 2011

Objective: Clinical trials of β-carotene supplementation and recent large-scale prospective studies have called into question the protective effects of vegetable and fruit consumption against lung cancer. To re-assess this issue, we reviewed data from Japanese epidemiological studies.
Methods: Original data were obtained from searches of MEDLINE and the Japana Centra Revuo Medicina (Ichushi) database. The associations were assessed based on their magnitude and the strength of the evidence, together with their biological plausibility as previously evaluated by the International Agency for Research on Cancer.
Results: We identified six cohort studies and four case–control studies on the consumption of vegetables and/or fruit. We focused on fruit and green-yellow vegetables as food items, as they were included in more of the studies, and insufficient data were available on other types of vegetables. Among the three cohort and two case–control studies that reported on green-yellow vegetables, only one of each study type showed a weak inverse association between lung cancer risk and their consumption. Two of the four cohort studies and one (or possibly two) of the four case–control studies demonstrated a weak inverse correlation between lung cancer risk and fruit consumption. Meta-analysis for fruit consumption revealed a summary relative risk that was significantly smaller than unity.
Conclusions: Our analysis of the Japanese epidemiological data showed that fruit consumption possibly decreased the risk of lung cancer, but found insufficient evidence of a link with vegetable consumption. Further prospective studies should assess the effects of consuming these food groups.

Key words: systematic review – vegetables – fruit – lung neoplasms – Japanese

INTRODUCTION

The protective effects of vegetable and fruit consumption against the development of lung cancer have previously been examined in case–control and cohort studies (1,2). There has been particular interest in the potential of vegetables that are rich in carotenoids to reduce the lung cancer risk. An international review by the World Cancer Research Fund and the American Institute for Cancer Research (3) concluded that the consumption of fruit and foods containing carotenoids probably decreased the risk of lung cancer, and that the consumption of non-starchy vegetables possibly decreased the risk (the evidence was classified as 'limited–suggestive'). This was in agreement with a review by the International Agency for Research on Cancer (IARC) (1), which found that a high intake of fruit and vegetables was associated with a decreased risk of lung cancer, based on meta-analyses of cohort and case–control studies.

Clinical trials of β-carotene supplementation, however, failed to show a decrease in the risk of lung cancer (4). In addition, the hypothesized risk reduction in relation to the consumption of vegetables has been challenged in some recent large-scale prospective studies (1).

A re-assessment of the role of the consumption of vegetables and fruit in the prevention of lung cancer in Japan is thus needed. Here, we reviewed the published epidemiological studies on the association of vegetable and fruit consumption with the risk of lung cancer among the Japanese population. This report is part of a series of review articles published by our research group investigating the association between health-related lifestyle factors (e.g. tobacco smoking, alcohol consumption and diet) and the risk of total cancers, as well as the major sites of cancer among the Japanese population (5).

METHODS

Identification of Eligible Studies

A MEDLINE search was conducted to identify epidemiological studies on the association between the consumption of vegetables and/or fruit and the risk of lung cancer that were published between 1980 and 2009. A search of the Japana Centra Revuo Medicina (Ichushi) database was also conducted to identify any such studies that were published in Japanese between 1983 and 2009. The query term used for the searches was 'lung cancer AND (vegetables OR fruit) AND Japan AND (case-control OR cohort studies)'. In addition, we manually searched through references from relevant articles where necessary. Papers written in either English or Japanese were reviewed, but only studies on Japanese individuals living in Japan were included. In the case of multiple publications analysing the same or overlapping datasets, only the largest study that included smoking as a confounding factor was included, because smoking is the best established risk factor for lung cancer (6). The individual reports are summarized separately in tabular form in the present report according to their design as cohort or case–control studies.

Evaluation of Results from Individual Studies

We evaluated the study results based on the magnitude of the association and the strength of the evidence. The food items assessed varied greatly among the studies. They included both individual food items (e.g. carrots and tomatoes) and food groups (e.g. green-yellow vegetables and fruit). Because the hazard ratios (HRs) and odds ratios (ORs) for different food items cannot be mutually compared, we extracted data for food items that were common to at least three studies and summarized them in the tables of the present report. It should be noted that in one cohort study (7), the HRs were approximated by the rate ratios. Green-yellow vegetables and fruit were found to satisfy the criteria mentioned above.

To evaluate the magnitude of the association, we used the HRs or ORs among all men and/or women. When estimates only for subgroups were available (e.g. ORs by histological type), we conducted a meta-analysis to obtain the summary measures for all men and/or women. General variance-based methods were used to estimate the summary statistics and their 95% confidence intervals (CIs). Heterogeneity among the studies was tested using the Q statistic to determine the summary HR or OR (i.e. a random- or fixed-effect model was selected according to the significance of the Q statistic). The meta-analysis was performed using the 'meta' command of the STATA statistical package, version 11.1 (Stata Corporation, College Station, TX, USA). Two-sided P-values < 0.05 were considered statistically significant.

The HRs or ORs for men and/or women in each epidemiological study were classified by the magnitude of their association, while also considering the statistical significance (SS) or non-significance (NS), as in our previous report (5). In brief, the HRs or ORs were grouped into the following four categories: 'strong' (denoted by ↑↑↑ or ↓↓↓) when HR or OR >2.0 (SS), or HR or OR <0.5 (SS); 'moderate' (denoted by ↑↑ or ↓↓) when HR or OR >2.0 (NS), $1.5 <$ HR or OR ≤ 2.0 (SS), $0.5 \leq$ HR or OR < 0.67 (SS), or HR or OR < 0.5 (NS); 'weak' (denoted by ↑ or ↓) when $1.5 <$ HR or OR ≤ 2.0 (NS), $0.67 \leq$ HR or OR ≤ 1.5 (SS), or $0.5 \leq$ HR or OR < 0.67 (NS); and 'no association' (denoted by '—') when $0.67 \leq$ HR or OR ≤ 1.5 (NS). Upward arrow symbols indicate a positive association, whereas downward arrow symbols indicate an inverse association.

In cases where the frequency or amount of food consumption had been separated into levels in a study, we mainly used the HR or OR derived from comparing the highest intake with the lowest. To consider the intermediate categories of intake, however, the P value for the trend was also taken into account when judging the SS. In other words, a study was defined as having SS if either the HR or the OR

Table 1. Lung cancer risk and consumption of vegetables and fruit in cohort studies of Japanese populations

Reference	Study period	Study population: Number of subjects for analysis	Study population: Source of subjects	Study population: Event followed	Study population: Number of incident cases or deaths	Food item	Category	Number among cases	HR (95% CI)	*P* for trend	Confounding variables considered	Comments
Hirayama (7)	1966–1982	122 261 men	General population	Death	1454 men	GYV	Daily		1.00	0.003	Age	HR: figures in parentheses show 90% CIs.
							Occasional		1.17 (1.07–1.29)			
							Rare		1.25 (0.95–1.65)			
							None		1.28 (0.64–2.56)			
		142 857 women			463 women	GYV	Daily		1.00	0.59		HR: figures in parentheses show 90% CIs.
							Occasional		1.22 (1.03–1.44)			
							Rare		0.25 (0.08–0.75)			
							None		0.87 (0.18–4.24)			
Ozasa et al. (10)	1988–1997	42 940 men	Participants in health check-ups, general population or other	Death	446 men	Green-leafy vegetables	≤1–2/week	164	1.00	0.035	Age, family history of lung cancer, and smoking	
							3–4/week	118	0.90 (0.71–1.14)			
							Almost every day	106	0.76 (0.59–0.98)			
						Carrots and squashes	≤1–2/month	96	1.00	0.35		
							1–2/week	114	0.71 (0.54–0.94)			
							3–4/week +	137	0.84 (0.64–1.10)			
						Tomatoes	≤1–2/month	163	1.00	0.32		
							1–2/week	85	0.70 (0.54–0.92)			
							3–4/week +	114	0.90 (0.70–1.16)			
						Oranges	≤1–2/month	87	1.00	0.041		
							1–2/week	86	0.88 (0.65–1.19)			
							3–4/week +	148	0.75 (0.57–0.99)			
						Fruit other than oranges	≤1–2/month	81	1.00	0.049		
							1–2/week	78	0.71 (0.52–0.98)			
							3–4/week +	141	0.73 (0.55–0.97)			
						Fruit juice	≤1–2/month	139	1.00	0.35		

Continued

Table 1. *Continued*

Reference	Study period	Study population: Number of subjects for analysis	Study population: Source of subjects	Study population: Event followed	Study population: Number of incident cases or deaths	Food item	Category	Number among cases	HR (95% CI)	*P* for trend	Confounding variables considered	Comments
							1–2/week	53	0.70 (0.51–0.96)			
							3–4/week +	91	0.90 (0.69–1.18)			
		55 308 women			126 women	Green-leafy vegetables	≤1–2/week	32	1.00	0.45		
							3–4/week	35	1.18 (0.73–1.91)			
							Almost every day	41	1.19 (0.75–1.90)			
						Carrots and squashes	≤1–2/month	11	1.00	0.69		
							1–2/week	36	1.33 (0.67–2.62)			
							3–4/week +	52	1.24 (0.64–2.41)			
						Tomatoes	≤1–2/month	36	1.00	0.37		
							1–2/week	22	0.75 (0.44–1.28)			
							3–4/week +	47	1.21 (0.76–1.94)			
						Oranges	≤1–2/month	12	1.00	0.63		
							1–2/week	16	0.92 (0.43–1.97)			
							3–4/week +	64	1.10 (0.58–2.09)			
						Fruit other than oranges	≤1–2/month	13	1.00	0.66		
							1–2/week	15	0.71 (0.33–1.51)			
							3–4/week +	56	0.80 (0.42–1.50)			
						Fruit juice	≤1–2/month	33	1.00	0.90		
							1–2/week	18	1.16 (0.65–2.07)			
							3–4/week +	24	0.95 (0.56–1.63)			
Takezaki et al. (11)	1985–1999	5885 men and women	General population	Incidence	51 men and women	GYV	<3/week	12	1.00	0.93	Age, sex, smoking and occupation	
							3–4/week	19	1.18 (0.57–2.43)			
							5/week +	20	1.06 (0.52–2.16)			
						Light-coloured vegetables	<3/week	14	1.00	0.30		
							3–4/week	13	0.94 (0.44–2.00)			
							5/week +	24	0.72 (0.37–1.40)			
						Fruit	<3/week	21	1.00	0.23		
							3–4/week	20	0.97 (0.52–1.79)			

							5/week +	10	0.61 (0.29–1.30)			
Sauvaget et al. (12)	1980–1998	38 540 men and women	Atomic-bomb survivors and non-exposed controls	Death	563 men and women	GYV	0–1/week	214	1.00	0.68	Age, sex, radiation dose, city, BMI, smoking, alcohol drinking habits and education	Daily fruit consumption was associated with a significant 32% reduced risk in men, but no association was found in women.
							2–4/week	225	0.98 (0.81–1.18)			
							Daily	124	0.95 (0.76–1.19)			
						Fruit	0–1/week	184	1.00	0.035		
							2–4/week	180	0.87 (0.71–1.08)			
							Daily	199	0.80 (0.65–0.98)			
Liu et al. (13)	1990–1999	93 338 men and women	General population	Incidence	428 men and women	Vegetables	T1	159	1.00		Age, sex, study area, exercise, BMI, consumption of salted foods, use of vitamin supplements, alcohol intake and smoking	The pooled HR was not computed due to the heterogeneity of HR for T2 of fruit consumption in cases of AD between two cohorts.
							T2	126	0.96 (0.76–1.23)			
							T3	143	1.03 (0.81–1.30)			
						Fruit	T1	164	1.00			
							T2	145	1.08 (0.64–1.81)			
							T3	119	1.16 (0.84–1.58)			
						Vegetables and fruit	T1	161	1.00			
							T2	137	0.97 (0.76–1.23)			
							T3	130	1.10 (0.79–1.52)			
					198 cases of AD	Vegetables	T1	62	1.00	0.24		
							T2	65	1.25 (0.70–2.23)			
							T3	71	1.13 (0.66–1.94)			
						Fruit	T1	67	1.00	0.27		
							T2	70	2.06/0.88			
							T3	61	1.40 (0.79–2.48)			
						Vegetables and fruit	T1	68	1.00	0.33		
							T2	64	1.01 (0.61–1.67)			
							T3	66	1.02 (0.56–1.87)			
					176 cases of non-AD	Vegetables	T1	77	1.00	0.21		
							T2	48	0.80 (0.55–1.16)			

Continued

Table 1. *Continued*

Reference	Study period	Study population: Number of subjects for analysis	Study population: Source of subjects	Study population: Event followed	Study population: Number of incident cases or deaths	Food item	Category	Number among cases	HR (95% CI)	*P* for trend	Confounding variables considered	Comments
							T3	51	0.79 (0.55–1.16)			
						Fruit	T1	79	1.00	0.99		
							T2	51	0.76 (0.46–1.24)			
							T3	46	0.96 (0.62–1.49)			
						Vegetables and fruit	T1	76	1.00	0.35		
							T2	55	0.81 (0.57–1.17)			
							T3	45	0.85 (0.57–1.25)			
Khan et al. (14)	1984–2002	1524 men	General population (randomly sampled)	Death	41 men	Raw GYV	Several times/ week+ vs. ≤several times/month		0.7 (0.4–1.3)			
						Raw WPV			1.3 (0.6–2.8)		Age and smoking	
						Cooked GYV			0.8 (0.4–1.9)			
						Cooked WPV			0.9 (0.4–2.1)			
						Fruit			0.8 (0.3–2.2)			
		1634 women			10 women	Raw GYV	Several times/ week+ vs. ≤several times/month		1.9 (0.4–8.9)			
						Raw WPV			1.5 (0.3–7.4)		Age, health status, health education, screening and smoking	
						Cooked GYV			1.1 (0.1–8.5)			
						Cooked WPV			1.1 (0.1–8.6)			

CI, confidence interval; T1-T3, tertiles 1–3; AD, adenocarcinoma; GYV, green-yellow vegetables; WPV, white-pale vegetables; HR, hazard ratio; BMI, body mass index.

Table 2. Lung cancer risk and consumption of vegetables and fruit in case-control studies of Japanese populations

Reference	Study period	Study subjects: Type and source	Definition	Number of cases	Number of controls	Food item	Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
Shimizu (15)	1975–1981	Hospital-based (Aichi Cancer Center)	Cases: microscopically confirmed. Controls: first-visit to outpatients without cancer.	63 cases of Kreyberg Group I (men and women)	63 controls (men and women)	Vegetables	Every day vs. less	0.8 (NS)		Matched (1:1) for sex, age (± 5 years), date of interview (as near as possible) and residence
						Fruits	≤2/week	1.0		
							3–6/week	0.8 (NS)		
							Every day	0.8 (NS)		
				36 cases of Kreyberg Group II (men and women)	36 controls (men and women)	Vegetables	Every day vs. less	0.5 (NS)		
						Fruits	≤2/week	1.0		
							3–6/week	0.3 (NS)		
							Every day	0.2 (NS)		
Shimizu et al. (16)	1982–1985	Hospital-based (four hospitals in Nagoya)	Cases: pathologically identified. Controls: in-patients without lung cancer.	90 female never smokers	163 female never smokers	Green-yellow vegetables	<3/week	1.0		Matched (1:2) for hospital, age (± 1 year) and date of admission
							≥3/week	0.9 (NS)		
						Fruit	<3/week	1.0		
							≥3/week	1.2 (NS)		
						Oranges (mandarin)	<8/week	1.0		
							≥8/week	1.0 (NS)		
Takezaki et al. (17)	1988–1997	Hospital-based (Aichi Cancer Center)	Cases: histologically diagnosed. Controls: first-visit to outpatients without cancer.	367 male cases of AD	2964 men	Raw vegetables	Almost never	1.00	0.66	Age, season and year of visit, occupation, prior lung diseases, smoking, and consumption of green vegetables and meat
							Occasionally	1.13 (0.69–1.85)		
							3–4/week	1.13 (0.69–1.86)		
							Every day	1.01 (0.62–1.65)		
						Green vegetables	<1/week	1.00	0.041	
							1–2/week	1.21 (0.88–1.67)		

Continued

Table 2. *Continued*

Reference	Study period	Study subjects: Type and source	Study subjects: Definition	Study subjects: Number of cases	Study subjects: Number of controls	Food item	Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
							3–4/week	0.90 (0.63–1.28)		
							5/week +	0.77 (0.51–1.15)		
						Carrots	<1/week	1.00	0.64	
							1–2/week	1.27 (0.97–1.65)		
							3–4/week	1.04 (0.71–1.51)		
							5/week +	1.08 (0.67–1.76)		
						Pumpkin	<1/week	1.00	0.68	
							1–2/week	1.23 (0.96–1.59)		
							3–4/week	0.87 (0.49–1.53)		
							5/week +	0.84 (0.32–2.16)		
						Fruit	Almost never	1.00	0.38	
							Occasionally	1.17 (0.75–1.85)		
							3–4/week	1.02 (0.63–1.65)		
							Every day	0.98 (0.61–1.58)		
				381 male cases of SQ + SM	2964 men	Raw vegetables	Almost never	1.00	0.004	
							Occasionally	1.31 (0.84–2.03)		
							3–4/week	0.70 (0.44–1.12)		
							Every day	0.80 (0.51–1.25)		
						Green vegetables	<1/week	1.00	0.002	
							1–2/week	0.95 (0.69–1.30)		
							3–4/week	0.90 (0.64–1.27)		
							5/week +	0.49 (0.32–0.74)		
						Carrots	<1/week	1.00	0.02	
							1–2/week	1.00 (0.76–1.31)		
							3–4/week	1.61 (1.12–2.31)		
							5/week +	1.49 (0.94–2.36)		
						Pumpkin	<1/week	1.00	0.036	
							1–2/week	1.20 (0.93–1.57)		
							3–4/week	1.67 (1.06–2.62)		

			5/week +	1.23 (0.55–2.77)	
		Fruit	Almost never	1.00	0.007
			Occasionally	0.88 (0.58–1.34)	
			3–4/week	0.81 (0.52–1.26)	
			Every day	0.61 (0.40–0.95)	
240 female cases of AD	1189 women	Raw vegetables	Almost never	1.00	0.9
			Occasionally	0.74 (0.39–1.41)	
			3–4/week	0.85 (0.45–1.60)	
			Every day	0.84 (0.45–1.55)	
		Green vegetables	<1/week	1.00	0.23
			1–2/week	0.83 (0.47–1.45)	
			3–4/week	1.09 (0.63–1.88)	
			5/week +	0.64 (0.36–1.15)	
		Carrots	<1/week	1.00	0.014
			1–2/week	0.76 (0.49–1.19)	
			3–4/week	0.70 (0.43–1.12)	
			5/week +	0.50 (0.29–0.86)	
		Pumpkin	<1/week	1.00	0.56
			1–2/week	0.93 (0.67–1.28)	
			3–4/week	1.02 (0.66–1.58)	
			5/week +	0.64 (0.28–1.48)	
		Fruit	Almost never	1.00	0.54
			Occasionally	0.71 (0.28–1.82)	
			3–4/week	0.78 (0.31–1.97)	
			Every day	0.68 (0.27–1.70)	
57 female cases of SQ + SM	1189 women	Raw vegetables	Almost never	1.00	0.9
			Occasionally	0.97 (0.26–3.55)	
			3–4/week	2.11 (0.61–7.34)	
			Every day	1.01 (0.28–3.58)	
		Green vegetables	<1/week	1.00	0.31
			1–2/week	0.83 (0.28–2.42)	
			3–4/week	1.00 (0.34–2.89)	

Continued