Information on covariates included in multivariate analyses, such as smoking, body mass index, history of hypertension, history of diabetes, and leisure-time sports or physical exercise, was also obtained from the same questionnaire at the baseline survey in each study.

Statistical analysis

Person-years of follow-up were calculated starting from the date of the baseline survey in each study until the date of death or end of follow-up, whichever came first. We conducted separate analyses by sex. Each study estimated the HRs and their 2-sided 95% CIs for total cancer associated with each alcohol intake consumption category, by using a Cox proportional hazards model. The studies estimated age (years, continuous)-adjusted and area-adjusted (in JPHC-I, JPHC-II and JACC only) HRs. Additional multivariate adjustments were made for smoking (never smoker, past smoker, current smoker (men: 1–19 cigarettes/day, ≥20 cigarettes/day; women: current)), body mass index (<18.5, 18.5–<25, ≥25), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (less than almost daily, almost daily), in addition to adjustment by age and area. We conducted further analysis that excluded deaths within 5 years of baseline and, in men, stratified analysis by smoking status (never smokers vs. current smokers). In addition, using four of these cohorts, namely, JPHC-II, JACC, MIYAGI and OHSAKI, we estimated risks in ex-drinkers and never-drinkers. An indicator term for missing data was created for each covariate. SAS V.9.1 and Stata V.11 were used for calculating the estimates.

A random-effects model was used to obtain a single pooled estimate of the HRs from the individual studies for each category.[24] The study-specific HRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component.[24] 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 per 15 g increase in alcohol intake and its SE. These values from the individual studies were then combined using a random-effects model. We tested for and quantified the heterogeneity of the HRs for the highest category and the trend association of alcohol consumption association among studies by using the I^2 statistic. Stata was used for the meta-analysis.

In addition, to express the impact of alcohol drinking on the risk of mortality, the population attributable fraction (PAF) (%) was estimated as pd(HR−1)/HR, where pd is the proportion of cases exposed to the risk factors.[25]

RESULTS

The present study included six ongoing large-scale population-based prospective cohorts comprising 309 082 subjects (144 012 men and 165 070 women) and 35 801 deaths (22 260 men and 13 541 women), including 13 274 deaths (37%) from cancer (8584 men and 4690 women), 4809 (13%) from heart disease (2831 men and 1978 women) and 4275 (12%) from cerebrovascular disease (2376 men and 1899 women) during 3 832 285 person-years of follow-up (average follow-up period: 12.4 years) (table 1).

Overall, 23% of men were non-drinkers; 44% habitually drank more than 23 g of alcohol per day and 3% more than 92 g. In women, 3% drank more than 23 g/day and 73% were non-drinkers.

Tables 2 and 3 show the pooled multivariate-adjusted HRs for all-cause mortality and mortality for cancer, heart disease and cerebrovascular disease associated with alcohol consumption.

All-cause mortality

In men (table 2), a U-shaped association was found. More specifically, there was a significantly lower all-cause mortality risk among subjects consuming <69 g/day, as compared with non-drinkers; there was no significant association in higher consumption categories. Similar patterns were observed when deaths within 5 years after baseline were excluded from the analysis and in stratified analyses by smoking status. In the analysis comparing ex-drinkers and never-drinkers, the HR of ex-drinkers was significantly higher than that of never-drinkers. Moreover, when compared with never-drinkers, an increase in risk was clearly observed in higher alcohol consumption categories.

In women (table 3), a similar U-shaped pattern was seen. The analysis comparing ex-drinkers and never-drinkers showed that, as compared with never-drinkers, the HR for ex-drinkers was significantly higher.

Cancer mortality

In men (table 2), a J-shaped pattern was observed, in which there was a significantly lower risk in subjects consuming <46 g/day, as compared with non-drinkers, and a significantly higher risk associated with the highest consumption category. Similar patterns were observed when deaths within 5 years after baseline were excluded from the analysis and in stratified analyses by smoking status. In the subgroup analysis of ex-drinkers and never-drinkers, the HR for ex-drinkers was significantly higher than that of never-drinkers, and the increased risk was clear in the highest alcohol consumption category when compared with that of never-drinkers. In women (table 3), no significant U-shaped pattern was found, except for the significantly increased risk in ex-drinkers.

Heart disease mortality

In men (table 2), heart disease mortality risk displayed a U-shaped pattern. There was a significantly lower risk in subjects consuming <69 g/day, as compared with non-drinkers. Similar patterns were observed when deaths within 5 years after baseline were excluded from the analysis, when analyses were stratified by smoking status, and when the analysis distinguished between ex-drinkers and never-drinkers, the former of which had a significantly higher risk than did the latter. In women (table 3), heart disease mortality followed a J-shaped pattern, with a significantly higher risk in those consuming ≥46 g/day of alcohol.

Cerebrovascular disease mortality

In men (table 2), cerebrovascular disease mortality followed a J-shaped pattern, with a lower risk in subjects consuming <46 g/day, as compared with non-drinkers, and a higher risk in those consuming ≥69 g/day. Similar patterns were observed when deaths within 5 years after baseline were excluded from the analysis, when analyses were stratified by smoking status, and when the analysis distinguished between ex-drinkers and never-drinkers, the former of which had a significantly higher risk than did the latter.

In women (table 3), there was no significant J-shaped association.

Population attributable fraction

Using estimated pooled HRs, we estimated the PAF attributable to alcohol consumption of ≥23 g/day and ≥46 g/day when subjects in these alcohol consumption categories decreased their consumption to <23 g/day and <46 g/day. In calculating these

Table 2 Pooled HRs for all-cause and major causes of mortality according to alcohol consumption category (men)*

	Non-drinkers (Never- and ex-drinkers)		Occasional drinkers (<once/week)	Current drinkers (≥once/week)					Trend (per 15 g increase)		Heterogeneity p value and I^2 (%)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	<23 g/day HR (95% CI)	23 to <46 g/day HR (95% CI)	46 to <69 g/day HR (95% CI)	69 to <92 g/day HR (95% CI)	≥92 g/day HR (95% CI)	HR (95% CI)	p Value for trend	For trend	For the highest category
Number of subjects (n=144012)	33597		10818	35698	34687	16819	7784	4609				
All-cause mortality												
Person-years (n=1740228)	404216		130675	425730	420603	212877	95516	50613				
Number of cases (n=22260)	7467		1157	4388	4830	2552	1226	640				
HR, age- and area-adjusted‡	1.00 (Reference)		**0.68 (0.64 to 0.73)**	**0.73 (0.67 to 0.79)**	**0.81 (0.74 to 0.89)**	0.91 (0.80 to 1.04)	1.24 (0.98 to 1.57)	1.22 (0.95 to 1.56)	**1.01 (1.00 to 1.02)**	**0.002**	<0.001 89.2%	<0.001 87.2%
HR, multivariate-adjusted§	1.00 (Reference)		**0.70 (0.65 to 0.74)**	**0.74 (0.69 to 0.79)**	**0.78 (0.72 to 0.85)**	0.86 (0.76 to 0.96)	1.13 (0.91 to 1.41)	1.12 (0.90 to 1.40)	1.01 (1.00 to 1.01)	0.073	<0.001 81.4%	<0.001 84.1%
	(Never)	(Ex)										
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.60 (1.46 to 1.75)**	**0.81 (0.75 to 0.87)**	**0.87 (0.77 to 0.98)**	0.92 (0.81 to 1.05)	1.05 (0.90 to 1.22)	**1.58 (1.11 to 2.26)**	**1.42 (1.08 to 1.87)**				
HR, excluding early deaths§	1.00 (Reference)		**0.72 (0.67 to 0.77)**	**0.80 (0.75 to 0.84)**	**0.86 (0.80 to 0.92)**	0.92 (0.82 to 1.04)	1.10 (0.94 to 1.29)	**1.27 (1.09 to 1.48)**	**1.01 (1.00 to 1.02)**	**0.004**	<0.001 80.8%	0.072 57.1%
HR, never smokers§	1.00 (Reference)		**0.63 (0.42 to 0.95)**	**0.67 (0.59 to 0.76)**	**0.77 (0.66 to 0.89)**	0.83 (0.68 to 1.01)	1.20 (0.83 to 1.73)	1.17 (0.90 to 1.52)	1.00 (0.99 to 1.02)	0.527	0.030 59.6%	0.335 11.7%
HR, current smokers§	1.00 (Reference)		**0.72 (0.65 to 0.81)**	**0.85 (0.77 to 0.95)**	**0.91 (0.84 to 0.99)**	0.96 (0.86 to 1.07)	1.20 (0.98 to 1.45)	**1.28 (1.03 to 1.58)**	**1.01 (1.01 to 1.02)**	**0.001**	<0.001 81.7%	0.014 71.9%
Cause-specific mortality												
Person-years (n=1675062)	389833		126530	401320	399898	211765	95105	50613				
Cancer												
Number of cases (n=8584)	2648		446	1712	1911	1099	511	257				
HR, age- and area-adjusted‡	1.00 (Reference)		**0.74 (0.67 to 0.82)**	**0.83 (0.78 to 0.90)**	**0.92 (0.87 to 0.98)**	1.02 (0.94 to 1.10)	**1.19 (1.00 to 1.42)**	**1.35 (1.17 to 1.56)**	**1.01 (1.00 to 1.02)**	**0.009**	<0.001 87.3%	0.360 6.6%
HR, multivariate-adjusted§	1.00 (Reference)		**0.75 (0.68 to 0.84)**	**0.86 (0.79 to 0.92)**	**0.91 (0.84 to 0.98)**	0.95 (0.88 to 1.03)	1.12 (0.94 to 1.33)	**1.24 (1.08 to 1.42)**	1.01 (0.999 to 1.01)	0.084	0.009 67.4%	0.423 0.0%
	(Never)	(Ex)										
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.40 (1.21 to 1.62)**	**0.86 (0.76 to 0.97)**	**0.92 (0.85 to 0.995)**	1.02 (0.95 to 1.10)	1.07 (0.98 to 1.17)	1.20 (0.94 to 1.55)	**1.43 (1.20 to 1.70)**				
HR, excluding early deaths§	1.00 (Reference)		**0.79 (0.70 to 0.89)**	0.96 (0.88 to 1.05)	1.01 (0.91 to 1.11)	1.02 (0.93 to 1.11)	**1.21 (1.08 to 1.36)**	**1.38 (1.17 to 1.62)**	**1.01 (1.00 to 1.02)**	**0.037**	0.003 71.9%	0.883 0.0%
HR, never smokers§	1.00 (Reference)		**0.79 (0.62 to 0.998)**	**0.75 (0.58 to 0.97)**	**0.82 (0.69 to 0.98)**	**0.71 (0.52 to 0.96)**	1.18 (0.65 to 2.13)	1.21 (0.82 to 1.79)	1.00 (0.99 to 1.01)	0.983	0.977 0.0%	0.888 0.0%
HR, current smokers§	1.00 (Reference)		**0.82 (0.69 to 0.97)**	0.94 (0.86 to 1.03)	0.98 (0.89 to 1.07)	1.09 (0.99 to 1.20)	**1.23 (1.02 to 1.48)**	**1.39 (1.18 to 1.65)**	**1.01 (1.00 to 1.02)**	**0.020**	<0.001 78.3%	0.467 0.0%
Heart disease												
Number of cases (n=2831)	1054		144	533	575	297	142	86				
HR, age- and area-adjusted‡	1.00 (Reference)		**0.63 (0.53 to 0.76)**	**0.65 (0.51 to 0.83)**	**0.70 (0.61 to 0.80)**	**0.72 (0.63 to 0.82)**	0.86 (0.59 to 1.26)	1.07 (0.82 to 1.41)	1.00 (0.99 to 1.00)	0.526	0.408 1.3%	0.287 20.5%

Continued

Table 2 Continued

	Non-drinkers (Never- and ex-drinkers)		Occasional drinkers (<once/week)	Current drinkers (≥once/week)					Trend (per 15 g increase)		Heterogeneity p value and I^2 (%)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	<23 g/day HR (95% CI)	23 to <46 g/day HR (95% CI)	46 to <69 g/day HR (95% CI)	69 to <92 g/day HR (95% CI)	≥92 g/day HR (95% CI)	HR (95% CI)	p Value for trend	For trend	For the highest category
HR, multivariate-adjusted§	1.00 (Reference)		**0.63 (0.53 to 0.76)**	**0.64 (0.50 to 0.83)**	**0.67 (0.57 to 0.77)**	**0.65 (0.54 to 0.78)**	0.79 (0.53 to 1.18)	0.93 (0.74 to 1.18)	0.99 (0.98 to 1.00)	0.199	0.072 50.7%	0.481 0.0%
	(Never)	(Ex)										
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.54 (1.34 to 1.77)**	**0.72 (0.57 to 0.90)**	0.82 (0.60 to 1.12)	**0.79 (0.65 to 0.97)**	0.79 (0.62 to 1.01)	1.10 (0.57 to 2.11)	1.10 (0.80 to 1.52)				
HR, excluding early deaths§	1.00 (Reference)		**0.65 (0.52 to 0.82)**	**0.73 (0.56 to 0.96)**	**0.75 (0.66 to 0.85)**	**0.70 (0.60 to 0.82)**	0.84 (0.62 to 1.15)	1.06 (0.80 to 1.40)	1.00 (0.99 to 1.01)	0.671	0.501 0.0%	0.522 0.0%
HR, never smokers§	1.00 (Reference)		**0.48 (0.29 to 0.79)**	**0.60 (0.40 to 0.89)**	0.77 (0.43 to 1.41)	0.55 (0.30 to 1.02)	1.37 (0.83 to 2.25)	1.36 (0.72 to 2.58)	1.01 (0.99 to 1.03)	0.249	0.369 7.4%	0.999 0.0%
HR, current smokers§	1.00 (Reference)		**0.73 (0.57 to 0.93)**	**0.71 (0.57 to 0.88)**	**0.75 (0.63 to 0.88)**	**0.77 (0.60 to 0.98)**	0.82 (0.54 to 1.24)	0.99 (0.71 to 1.38)	1.00 (0.99 to 1.01)	0.627	0.743 0.0%	0.289 20.1%
Cerebrovascular diseases												
Number of cases (n=2376)	786		113	453	503	302	154	65				
HR, age- and area-adjusted‡	1.00 (Reference)		0.89 (0.59 to 1.35)	0.82 (0.67 to 1.00)	**0.81 (0.66 to 0.98)**	1.03 (0.90 to 1.19)	**1.44 (1.20 to 1.73)**	**1.44 (1.03 to 2.02)**	1.01 (0.995 to 1.02)	0.191	0.008 68.0%	0.212 33.4%
HR, multivariate-adjusted§	1.00 (Reference)		0.92 (0.60 to 1.42)	**0.80 (0.65 to 0.97)**	**0.78 (0.64 to 0.95)**	0.98 (0.85 to 1.13)	**1.33 (1.10 to 1.60)**	1.29 (0.92 to 1.80)	1.00 (0.99 to 1.01)	0.703	0.099 46.1%	0.220 32.0%
	(Never)	(Ex)										
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.55 (1.04 to 2.31)**	1.02 (0.67 to 1.58)	0.92 (0.78 to 1.07)	0.84 (0.67 to 1.06)	**1.21 (1.02 to 1.43)**	**1.68 (1.34 to 2.10)**	**1.75 (1.02 to 3.02)**				
HR, excluding early deaths§	1.00 (Reference)		0.93 (0.52 to 1.67)	**0.77 (0.64 to 0.93)**	**0.79 (0.64 to 0.98)**	1.00 (0.80 to 1.23)	1.37 (0.85 to 2.20)	1.33 (0.86 to 2.06)	1.01 (0.99 to 1.03)	0.279	0.030 59.7%	0.146 44.2%
HR, never smokers§	1.00 (Reference)		0.74 (0.47 to 1.16)	**0.59 (0.44 to 0.78)**	0.74 (0.43 to 1.27)	1.16 (0.81 to 1.66)	1.26 (0.72 to 2.20)	1.94 (0.84 to 4.45)	1.00 (0.95 to 1.04)	0.820	0.063 52.2%	0.185 40.8%
HR, current smokers§	1.00 (Reference)		0.83 (0.44 to 1.56)	0.87 (0.66 to 1.14)	0.88 (0.74 to 1.04)	1.06 (0.76 to 1.48)	**1.46 (1.14 to 1.86)**	**1.69 (1.21 to 2.35)**	1.01 (0.996 to 1.03)	0.156	0.037 57.7%	0.911 0.0%

Numbers in boldface indicate $p<0.05$.

*The pooled analyses included the JPHC-I, JPHC–II, JACC, MIYAGI, OHSAKI and TAKAYAMA studies.

†The pooled analyses included the JPHC–II, JACC, MIYAGI and OHSAKI studies.

‡Adjusted for age (years, continuous) and area (JPHC-I, JPHC-II and JACC).

§Adjusted for smoking (never smoker, past smoker, current smoker of 1–19 cigarettes/day or ≥20 cigarettes/day), body mass index (<18.5, 18.5–<25, ≥25), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (<almost daily, almost daily), in addition to adjustment in ‡.

Table 3 Pooled HRs for all-cause and major causes of mortality according to alcohol consumption category (women)*

	Non-drinkers (Never- and ex-drinkers)		Occasional drinkers (<once/week)	Current drinkers (≥once/week)			Trend (per 15 g-increase)		Heterogeneity p Value and I^2 (%)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	<23 g/day HR (95% CI)	23 to <46 g/day HR (95% CI)	≥46 g/day HR (95% CI)	HR (95% CI)	p Value for trend	For trend	For the highest category
Number of subjects (n=165070)	120885		18468	20569	3559	1589				
All causes										
Person-years (n=2092057)	1574957		218893	240869	40144	17195				
Number of cases (n=13541)	11258		932	1041	220	90				
HR, age- and area-adjusted‡	1.00 (Reference)		**0.87 (0.80 to 0.95)**	**0.87 (0.80 to 0.95)**	1.16 (0.90 to 1.50)	**1.38 (1.12 to 1.70)**	**1.02 (1.01 to 1.02)**	**<0.001**	0.397 3.0%	0.559 0.0%
HR, multivariate-adjusted§	1.00 (Reference)		**0.87 (0.80 to 0.95)**	**0.85 (0.79 to 0.92)**	1.01 (0.80 to 1.28)	1.15 (0.93 to 1.42)	**1.01 (1.00 to 1.02)**	**0.010**	0.616 0.0%	0.696 0.0%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.38 (1.24 to 1.53)**	0.88 (0.77 to 1.00)	**0.88 (0.79 to 0.99)**	1.19 (0.86 to 1.63)	1.27 (0.97 to 1.66)				
HR, excluding early deaths§	1.00 (Reference)		**0.90 (0.81 to 0.998)**	**0.91 (0.85 to 0.98)**	1.06 (0.71 to 1.48)	1.21 (0.96 to 1.53)	1.01 (0.999 to 1.02)	0.097	0.819 0.0%	0.867 0.0%
Cause-specific mortality										
Person-years (n=2031281)	1529797		212405	232360	39598	17122				
Cancer										
Number of cases (n=4690)	3787		376	402	93	32				
HR, age- and area-adjusted‡	1.00 (Reference)		0.95 (0.81 to 1.11)	0.89 (0.75 to 1.06)	0.98 (0.70 to 1.38)	1.20 (0.84 to 1.70)	0.996 (0.98 to 1.01)	0.587	0.339 11.9%	0.890 0.0%
HR, multivariate-adjusted§	1.00 (Reference)		0.94 (0.81 to 1.09)	0.88 (0.73 to 1.05)	1.02 (0.81 to 1.29)	1.05 (0.73 to 1.50)	0.995 (0.98 to 1.01)	0.545	0.790 0.0%	0.746 0.0%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	**1.36 (1.12 to 1.67)**	0.95 (0.76 to 1.19)	0.90 (0.70 to 1.17)	1.00 (0.72 to 1.40)	1.06 (0.65 to 1.71)				
HR, excluding early deaths§	1.00 (Reference)		1.00 (0.87 to 1.15)	0.98 (0.82 to 1.18)	1.04 (0.72 to 1.50)	0.92 (0.57 to 1.47)	0.99 (0.96 to 1.03)	0.744	0.100 45.8%	0.502 0.0%
Heart disease										
Number of cases (n=1978)	1678		115	139	30	16				
HR, age- and area-adjusted‡	1.00 (Reference)		0.86 (0.70 to 1.05)	0.86 (0.72 to 1.04)	1.21 (0.81 to 1.82)	**2.11 (1.28 to 3.48)**	1.05 (0.98 to 1.12)	0.171	0.010 66.7%	0.789 0.0%
HR, multivariate-adjusted§	1.00 (Reference)		0.86 (0.70 to 1.06)	0.84 (0.69 to 1.01)	1.02 (0.70 to 1.49)	**1.73 (1.04 to 2.86)**	1.03 (0.96 to 1.10)	0.400	0.048 55.2%	0.584 0.0%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	1.02 (0.76 to 1.36)	0.78 (0.58 to 1.04)	0.77 (0.62 to 0.95)	1.01 (0.65 to 1.56)	1.57 (0.81 to 3.06)				
HR, excluding early deaths§	1.00 (Reference)		0.92 (0.66 to 1.27)	0.89 (0.64 to 1.24)	1.02 (0.64 to 1.60)	1.70 (0.93 to 3.11)	1.04 (0.99 to 1.08)	0.096	0.841 0.0%	0.813 0.0%
Cerebrovascular disease										
Number of cases (n=1899)	1592		117	145	27	18				
HR, age- and area-adjusted‡	1.00 (Reference)		0.86 (0.71 to 1.05)	0.94 (0.75 to 1.18)	0.92 (0.47 to 1.80)	**1.99 (1.24 to 3.18)**	1.02 (0.99 to 1.05)	0.315	0.062 52.4%	0.418 0.0%

Continued

Table 3 Continued

	Non-drinkers (Never- and ex-drinkers)		Occasional drinkers (<once/week)	Current drinkers (≥once/week)			Trend (per 15 g-increase)		Heterogeneity p Value and I^2 (%)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	<23 g/day HR (95% CI)	23 to <46 g/day HR (95% CI)	≥46 g/day HR (95% CI)	HR (95% CI)	p Value for trend	For trend	For the highest category
HR, multivariate-adjusted§	1.00 (Reference)		0.85 (0.70 to 1.03)	0.87 (0.72 to 1.04)	0.78 (0.43 to 1.44)	1.42 (0.81 to 2.49)	1.00 (0.96 to 1.04)	0.985	0.038 57.6%	0.277 20.8%
	(Never)	(Ex)								
HR, ex-drinkers distinguished †,§	1.00 (Reference)	1.00 (0.52 to 1.94)	0.85 (0.67 to 1.09)	0.90 (0.74 to 1.10)	1.03 (0.52 to 2.01)	1.24 (0.36 to 4.34)				
HR, excluding early deaths§	1.00 (Reference)		0.80 (0.62 to 1.02)	0.88 (0.71 to 1.09)	0.90 (0.56 to 1.45)	1.48 (0.72 to 3.07)	1.08 (0.89 to 1.30)	0.435	<0.001 97.4%	0.229 28.9%

Numbers in boldface indicate p<0.05.
*The pooled analyses included the JPHC-I, JPHC-II, JACC, MIYAGI, OHSAKI and TAKAYAMA studies.
†The pooled analyses included the JPHC-II, JACC, MIYAGI and OHSAKI studies.
‡Adjusted for age (years, continuous) and area (JPHC-I, JPHC-II and JACC).
§Adjusted for smoking (never smoker, past smoker, or current smoker), body mass index (<18.5, 18.5—<25, ≥25), history of hypertension (no, yes), history of diabetes (no, yes), and leisure-time sports or physical exercise (<almost daily, almost daily), in addition to adjustment in ‡.

estimates, we assumed that non-drinkers (never- and ex-drinkers) and occasional drinkers (<once/week) did not change their amount of alcohol consumption. The results indicate that, in men, 4.8% of total mortality, 3.1% of cancer mortality, 1.9% of heart disease mortality and 8.6% of cerebrovascular disease mortality could be prevented if current drinkers reduced their alcohol consumption to <23 g/day, and that 4.6% of total mortality, 2.9% of cancer mortality, 1.8% of heart disease mortality and 8.8% of cerebrovascular disease mortality could be prevented if current drinkers reduced their alcohol consumption to <46 g/day. In women, the PAFs were much lower than in men: 0% of total mortality, 0% of cancer mortality, 0.6% of heart disease mortality and 0.7% of cerebrovascular disease mortality could be prevented if female current drinkers reduced their alcohol consumption to <23 g/day, and 0.1% of total mortality, 0% of cancer mortality, 0.6% of heart disease mortality and 0.8% of cerebrovascular disease mortality could be prevented if current drinkers reduced their alcohol consumption to <46 g/day.

DISCUSSION

In this pooled analysis, we found J- or U-shaped associations between the amount of alcohol consumed and the risks of total and major causes of mortality in men, and the risks of total and heart disease mortality in women. When ex-drinkers were excluded from the baseline category, the HRs for the low drinkers were reduced and those for the high drinkers were increased. We confirmed that, overall, alcohol consumption of <46 g/day in male and <23 g/day in female Japanese was associated with a lower mortality risk than those for non-drinkers and heavy drinkers. A similar pattern was observed when deaths within 5 years after baseline were excluded from the analysis and when analysis was stratified by smoking status. In addition, mortality risk appeared to increase linearly with rising alcohol dose among drinkers. Using these estimates, we calculated that 5% of total mortality, 3% of cancer mortality, 2% of heart disease mortality and 9% of cerebrovascular disease mortality in men, but only 0–1% of these risks in women, could be prevented by reducing alcohol consumption to <46 g/day in men and <23 g/day in women.

The present study has several strengths. It included most of the ongoing, large-scale, prospective cohorts in Japan. In addition, the birth generation of the study subjects in the cohorts overlapped. Therefore, pooling of these cohorts allows for stable summary quantitative estimates of the effect of alcohol consumption on premature death in middle-aged and elderly Japanese adults. At the same time, because this study was not based on a meta-analysis of published studies, the possibility of publication bias is small. In the studies included in this pooled analysis, alcohol consumption was measured before death, which precludes the possibility of selection and recall bias. In addition, the categories for alcohol intake and the covariates used were identical among studies, which removes a potential source of heterogeneity that can occur when conducting a meta-analysis of published studies.

However, there are several limitations that warrant consideration. As our analyses were conducted using only a baseline questionnaire, we were unable to consider changes over time in alcohol intake. Also, we were unable to assess alcohol consumption by type of beverage. Because questions on alcohol consumption differed among studies, heterogeneity of the distribution of alcohol categories between the studies could not be distinguished from misclassification caused by measurement

error occurring in each study. In this pooled analysis, mortality was defined as an outcome; thus, it is difficult to distinguish whether alcohol consumption was associated with incidence, survival or both.

There is strong and consistent epidemiological evidence of a significant inverse association between low to moderate alcohol consumption and cardiovascular disease.[26] Alcohol consumption is linked to changes in several vascular and biochemical factors that have potential cardioprotective benefits. Alcohol consumption is believed to reduce the risk of cardiovascular events primarily by increasing high-density lipoprotein (HDL) cholesterol levels, decreasing platelet aggregation via inhibition of prostaglandin synthesis and changes in fibrinogen, and lowering levels of tissue-plasminogen activator (t-PA) and PA inhibitor (PAI-1).[27 28] However, the anticoagulant effect of alcohol, despite its beneficial effect on ischaemic stroke, may increase the risk of haemorrhagic stroke.[29–31]

Regarding cancer, the latest evaluation in 2007, by the International Agency for Research on Cancer, confirmed that alcoholic beverages are carcinogenic to humans (group 1) and concluded that the occurrence of certain sites of cancer, such as those of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and female breast, is causally related to alcohol consumption.[32 33] The association between alcohol and cancer may be the result of high acetaldehyde exposure, which is considered carcinogenic.[32] In addition, excessive alcohol intake impairs folate absorption and bioavailability by inhibiting expression of reduced folate carrier and decreasing hepatic uptake and renal conservation of circulating folate.[34] Decreased folate status can contribute to aberrant DNA synthesis and methylation, which may increase the risk of cancer.[35]

Our results suggest that there is a specific level of alcohol consumption with the least risk, which was observed among men consuming <46 g/day and women consuming <23 g/day. Also, in drinkers, the increase in cancer risk appeared to be linear with respect to the amount of alcohol consumed. A previous meta-analysis estimated that 2–4 drinks/day (20–40 g/day) in men and 1–2 drinks/day (10–20 g/day) in women was inversely associated with total mortality[1]; these values roughly accord with the estimates for the present Japanese population. However, approximately half of all Japanese have an ALDH2-deficient phenotype. ALDH2 is a key enzyme in the conversion of acetaldehyde to acetate,[36] and a deficiency in this enzyme results in greater acetaldehyde exposure.[37] The high prevalence of ALDH2 deficiency indicates a need for caution in interpreting the results for non-drinkers, and for never- and ex-drinkers, because some of these subjects were unable to drink because of this deficiency, which would result in risk inflation in this category. ALDH2 deficiency potentially increases not only the risk of alcohol-related diseases, including cancer, but also the fraction of mortality attributable to high alcohol drinking in the population with a high prevalence of this deficiency.

With regard to sex differences in the protective effect of alcohol, previous studies examined possible mechanisms for this difference.[1 2] Women have a higher blood alcohol concentration when men and women consume the same amount of alcohol.[38] Also, women metabolise ethanol differently and have lower gastric alcohol dehydrogenase activity, resulting in higher blood ethanol levels.[39] Women who consume moderate or high levels of alcohol have a higher risk than men of death from any cause, owing to their increased risk of cancer.[9] We could not assess this association in detail, especially among female heavy drinkers, because the proportion of such women was too small, even in pooled analysis.

What is already known on this subject

- A number of studies have suggested the health benefits of light to moderate alcohol consumption with respect to total and cardiovascular mortality, and the harmful effect of heavy alcohol drinking for certain sites of cancer.
- However, because published studies use different alcohol consumption categories, meta-analysis for the purpose of quantitative assessment is not possible.

What this study adds

This study confirmed that maintaining alcohol consumption below 46 g/day in men and below 23 g/day in women minimises the risks of total mortality and mortality from major diseases in the Japanese population.

Finally, regarding public policy implications, maintaining light to moderate alcohol consumption, specifically <46 g/day in men and <23 g/day in women, may be a feasible public health recommendation for the Japanese population. However, it might not be appropriate to recommend that non-drinkers begin drinking, because of the observed increase in risk with rising alcohol dose among drinkers, the high prevalence of ALDH2 deficiency in Japanese subjects, and the fact that many abstainers have good reasons to refrain from drinking.[40]

In conclusion, our results suggest that maintaining alcohol consumption at <46 g/day (2 *go*) in men and <23 g/day (1 *go*) in women may minimise the risks of total mortality and mortality from major diseases in the Japanese population.

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Public Health Report

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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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				Food item	Category	Number among cases	HR (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths							
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				Food item	Category	Number among cases	HR (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths							
							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				Food item	Category	Number among cases	HR (95% CI)	*P* for trend	Confounding variables considered	Comments
		Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths							
							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				Food item	Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls					
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				Food item	Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls					
							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

Table 2. *Continued*

Reference	Study period	Study subjects				Food item	Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls					
							5/week+	1.37 (0.46–4.09)		
						Carrots	<1/week	1.00	0.08	
							1–2/week	1.05 (0.46–2.41)		
							3–4/week	0.51 (0.19–1.40)		
							5/week+	0.47 (0.16–1.43)		
						Pumpkin	<1/week	1.00	0.82	
							1–2/week	0.81 (0.40–1.63)		
							3–4/week	0.78 (0.30–2.01)		
							5/week+	1.18 (0.32–4.30)		
						Fruit	Almost never	1.00	0.67	
							Occasionally	0.50 (0.11–2.31)		
							3–4/week	0.34 (0.07–1.60)		
							Every day	0.49 (0.11–2.13)		
Matsuo et al. (18)	2001–2005	Hospital-based (Aichi Cancer Center)	Cases: histologically diagnosed non-small-cell lung cancer cases. Controls: first-visit to outpatients without cancer.	122 female and male cases of lung cancer with *EGFR* mutation	1757 men and women	Green-yellow vegetables	T1	1.00	0.28	Age, sex, energy intake and smoking
							T2	1.06 (0.64–1.74)		
							T3	0.76 (0.45–1.29)		
						Other vegetables	T1	1.00	0.53	
							T2	0.81 (0.49–1.33)		
							T3	0.84 (0.51–1.37)		
						Fruit	T1	1.00	0.60	
							T2	0.93 (0.55–1.56)		
							T3	1.10 (0.66–1.85)		
				231 male and female cases of lung cancer without *EGFR* mutation	1757 men and women	Green-yellow vegetables	T1	1.00	0.044	
							T2	0.78 (0.56–1.10)		

	T3	0.69 (0.47–1.00)		
Other vegetables	T1	1.00	0.16	
	T2	0.72 (0.51–1.02)		
	T3	0.78 (0.53–1.11)		
Fruit	T1	1.00	0.096	
	T2	0.91 (0.65–1.27)		
	T3	0.72 (0.49–1.06)		

CI, confidence interval; NS, not significant; SQ, squamous cell carcinoma; AD, adenocarcinoma; SM, small cell carcinoma; *EGFR*, epidermal growth factor receptor; T1–T3, tertiles 1–3

for the highest intake category (versus the lowest) was statistically significant, or if the *P*-value for the trend was <0.05. If the trend *P* value was not available in an article, it was estimated from the HRs or ORs along with their 95% CIs by food-intake category. More specifically, the $\log_e$(HR) or $\log_e$(OR) was regressed on the intake score with the reciprocal of variance of the $\log_e$(HR) or $\log_e$(OR) in each intake category, derived from the CIs, used for weighting. The regression model was linear without an intercept, and the *P* value for its slope was considered as the trend *P* value. An intake score of 0, 1, 2, etc. was assigned from the lowest intake category through to the highest group. This estimate was also made with the STATA statistical package.

Meta-Analysis of Lung Cancer Risk and Fruit Consumption

Because inverse associations between lung cancer risk and fruit consumption were found across several cohort and case–control studies, we conducted a meta-analysis to investigate further. We used two types of analysis to estimate the summary relative risk (RR) for the highest versus lowest intake category and that per serving per day. The method described in the section on the 'Evaluation of results from individual studies' was used for the meta-analysis.

In the analysis of RR per serving per day, one serving was assumed to correspond to 80 g consumption, as in the review by the World Cancer Research Fund and the American Institute for Cancer Research (2). For each individual study, a variance-weighted log-linear regression analysis of the HRs or ORs was performed according to the mean, median or midpoint of fruit consumption, except in the case of studies that included only two exposure categories, for which the value of the logarithm of the HRs or ORs for one serving was used (8). The resultant figures per serving per day from individual studies were then synthesized to obtain the summary measure. To validate the results, we also made a sensitivity analysis using 70, 80, 90 and 100 g for one serving of fruit.

Overall Judgement on Strength of Evidence

The strength of the evidence was then evaluated by applying a method similar to that used in the World Health Organisation (WHO)/Food and Agriculture Organisation (FAO) Expert Consultation Report (9), in which evidence was classified as 'convincing', 'probable', 'possible' or 'insufficient'. We assumed that the biological plausibility, based on the evidence from experimental animals and mechanistic or other relevant data, corresponded to the judgment of the most recent evaluation from the IARC (1). Despite the use of this quantitative assessment procedure, an arbitrary assessment could not be avoided in cases where considerable variation existed in the magnitude of the associations reported between the results of different studies. Our final judgment was made based on a consensus of the

Table 3. Summary of associations between lung cancer risk and consumption of vegetables and fruit in cohort studies of Japanese populations

Reference	Study period	Study subjects					Green-yellow vegetables				Fruit			
		Sex	Number of subjects	Age (years)	Event	Number of incident cases or deaths	Magnitude of association[a]	HR (95% CI)	Intake categories	Trend *P*	Magnitude of association[a]	HR (95% CI)	Intake categories	Trend *P*
Hirayama (7)	1966–1982	Men	122 261	40+	Death	1454	↓	1.28 (0.56–2.92)	None vs. daily	0.003	NA			
		Women	142 857	40+	Death	463	—	0.87 (0.13–5.71)	None vs. daily	0.59	NA			
Ozasa et al. (10)	1988–1997	Men	42 940	40–79	Death	446	NA				NA			
		Women	55 308	40–79	Death	126	NA				NA			
Takezaki et al. (11)	1985–1999	Men and women	5885	30+	Incidence	51	—	1.06 (0.52–2.16)	5/week+ vs. <3/ week	0.93	↓	0.61 (0.29–1.30)	5/week+ vs. <3/ week	0.23
Sauvaget et al. (12)	1980–1998	Men and women	38 540	34–103	Death	563	—	0.95 (0.76–1.19)	Daily vs. 0–1/ week	0.68	↓	0.80 (0.65–0.98)	Daily vs. 0–1/ week	0.035
Liu et al. (13)	1990–1999	Men and women	93 338	40–69	Incidence	428	NA				—	1.16 (0.84–1.58)	T3 vs. T1	0.33[b]
Khan et al. (14)	1984–2002	Men	1524	40–97	Death	41	NA				—	0.8 (0.3–2.2)	Several times/ week+ vs. less	NA
		Women	1634	40–97	Death	10	Insufficient number of cases							

CI, confidence interval; NA, not available; T1–T3, tertiles 1–3; HR, hazard ratio.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; —, no association (see Methods for more detailed definitions).
[b]Estimated from HRs with their 95% CIs by food intake category (see Methods for details of the procedure).

research group members, and was therefore somewhat subjective. To assure the validity of our systematic review, the authors of the articles along with other members of our research group evaluated the evidence tables (Tables 1 and 2) and the summary tables (Tables 3 and 4), and our conclusions were based on a consensus. Details of our evaluation methods have been published elsewhere (5).

MAIN FEATURES AND COMMENTS

Evidence from Individual Studies

We identified six cohort studies (Table 1) (7,10–14) and four case–control studies (Table 2) (15–18) on lung cancer risk and the consumption of vegetables and/or fruit. In addition, we identified an article by Iso and Kubota (19) on a cohort study, the findings of which were also reported by Ozasa et al. (10); the former article was not included in the present review, however, because it did not take smoking into account as a confounding factor. Three case–control studies used overlapping data from one cancer hospital. From these, we selected the study by Takezaki et al. (17) to include in our review, because one of the other two studies did not consider smoking habits (20) and the other used a less comprehensive dataset (21). Of the six cohort studies, three (7,11,13) were population based, in which subjects were enrolled from general populations in geographically defined areas. The endpoint was defined as the incidence of lung cancer in two of these studies (11,13) and as death from the cancer in the other four (7,10,12,14). All four case–control studies were hospital based (i.e. cases were recruited from arbitrarily selected hospitals); the control subjects were also selected from among patients in hospitals where cases were identified in all of these investigations (i.e. hospital controls).

All (10–14,17,18) but one cohort (7) and one case–control (15) study controlled for possible confounding effects of smoking, or limited their participants to those who had never smoked (16). Among the six cohort studies, three

Table 4. Summary of associations between lung cancer risk and consumption of vegetables and fruit in case-control studies of Japanese populations

Reference	Study period	Study subjects				Green-yellow vegetables				Fruit			
		Sex	Age (years)	Number of cases	Number of controls	Magnitude of association[a]	OR (95% CI or *P*)	Intake categories	Trend *P*	Magnitude of association[a]	OR (95% CI or *P*)	Intake categories	Trend *P*
Shimizu (15)	1975–1981	Men and women	NA	99	99	NA				↓?	0.8 (Kreyberg I, NS) 0.2 (Kreyberg II, NS)	Every day vs. ≤2/week	NA
Shimizu et al. (16)	1982–1985	Women	35–81	90	163	—	0.9 (NS)	3/week+ vs. <3/week	NA	—	1.2 (NS)	3/week+ vs. <3/week	NA
Takezaki et al. (17)	1988–1997	Men	40–79	748	2964	NA				—	0.76 (0.55–1.04)[b]	Every day vs. almost never	0.089[c]
		Women	40–79	297	1189	NA				↓	0.62 (0.28–1.36)[b]	Every day vs. almost never	0.064[c]
Matsuo et al. (18)	2001–2005	Men and women	NA	353	1757	↓	0.71 (0.53–0.97)[b]	T3 vs. T1	0.016[c]	—	0.84 (0.62–1.14)[b]	T3 vs. T1	0.20[c]

CI, confidence interval; NA, not available; NS, not significant; T1–T3, tertiles 1–3; OR, odds ratio.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; —, no association (see Methods for more detailed definitions).
[b]Based on a meta-analysis.
[c]Estimated from ORs with their 95% CIs by food intake category (see Methods for more details of the procedure).

presented results by gender (7,10,14), while the other three combined data for both genders (11–13). One case–control study (17) reported results by gender, two (15,18) combined data from men and women and the last (16) included only women. As mentioned in the 'Evaluation of results from individual studies' section, green-yellow vegetables and fruit were selected as food items to be analysed, because their inclusion was relatively common among the studies. Sufficient data were not available for other types of vegetable or for vegetables as a group.

The magnitudes of the associations for green-yellow vegetables and fruit are summarized in Tables 3 and 4 for cohort and case–control studies, respectively. Three cohort studies (7,11,12) and two case–control studies (16,18) reported findings on green-yellow vegetables. Only one cohort study (7) and one case–control study (18) showed a weak inverse association (↓) between lung cancer risk and consumption of these vegetables. In the case of fruit, two (11,12) out of four cohort studies (11–14) and one (17) out of four case–control studies (15–18) demonstrated a weak inverse association (↓). Although one additional study by Shimizu (15) showed a similar correlation, its magnitude was unclear because insufficient data were provided in the article to obtain summary ORs for all histological types (↓? in Table 4).

Summary Measures for Lung Cancer Risk and Fruit Consumption

The summary RR was estimated to be 0.85 (95% CI = 0.75–0.96) for the highest versus lowest intake category and 0.92 (95% CI = 0.84–1.00) per serving per day (Fig. 1, $P < 0.05$ for both). The cohort studies and the case–control studies provided reasonably consistent summary measures, although they did not reach statistical significance for the former. The inverse association between fruit consumption and lung cancer risk was consistently detected in the sensitivity analysis using 70–100 g for one serving, although it was somewhat attenuated when one serving was assumed to be 70 g. The summary RR (95% CI) was 0.93 (0.86–1.01), 0.92 (0.84–1.00), 0.90 (0.82–0.99) and 0.89 (0.80–0.98) for 70, 80, 90 and 100 g of serving size, respectively (a fixed-effect model for all the serving sizes; test for heterogeneity by the Q statistic: $P \geq 0.05$ for all).

Methodological Issues in the Reviewed Studies

Some methodological issues should be kept in mind when assessing the findings from these cohort and case–control studies.