Table 1 Characteristics according to weight change categories at the 5-year follow-up survey

	Men					*Women*				
	⩾5 kg loss	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*⩾5 kg gain*	*⩾5 kg loss*	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*⩾5 kg gain*
No of subjects	3211	3307	22 232	3926	3544	3239	3906	29 108	4766	3072
Age (years), mean (s.d.)	57.7 (7.9)	57.6 (7.9)	56.5 (7.8)	55.3 (7.6)	55.4 (7.8)	58.9 (8.0)	58.5 (8.0)	56.8 (7.8)	55.0 (7.7)	55.4 (7.8)
Weight (kg), mean (s.d.)	60.7 (9.7)	61.8 (8.6)	62.7 (8.5)	66.3 (8.4)	69.4 (9.1)	51.5 (8.5)	52.1 (7.7)	53.5 (7.3)	56.7 (7.2)	60.6 (8.3)
BMI at baseline ($kg\,m^{-2}$), mean (s.d.)	25.2 (3.0)	24.2 (2.7)	23.3 (2.7)	23.2 (2.7)	23.0 (2.8)	25.6 (3.4)	24.0 (3.1)	23.2 (2.9)	23.0 (2.9)	23.1 (3.3)
BMI at 5-year survey ($kg\,m^{-2}$), mean (s.d.)	22.5 (3.0)	23.0 (2.7)	23.3 (2.7)	24.4 (2.7)	25.5 (3.0)	22.5 (3.4)	22.7 (3.1)	23.2 (3.0)	24.4 (2.9)	26.0 (3.4)
Weight change[a] (kg), mean (s.d.)	−7.5 (3.1)	−3.4 (0.5)	0.1 (1.3)	3.3 (0.5)	7.1 (2.7)	−7.4 (3.0)	−3.4 (0.5)	0.1 (1.3)	3.3 (0.5)	6.9 (2.6)
Weight change[b] (%), mean (s.d.)	−11.1 (4.5)	−5.2 (1.0)	0.1 (2.1)	5.4 (1.1)	11.7 (5.2)	−12.7 (5.1)	−6.2 (1.2)	0.2 (2.4)	6.4 (1.3)	13.3 (5.8)
BMI $\geqslant 25\,kg\,m^{-2}$ (%)	18.8	20.8	24.8	37.1	51.8	20.4	21.6	26.4	40.2	58.2
Smoking (%)										
Never	33.5	34.0	35.6	35.3	32.2	91.8	92.3	94.0	93.8	91.9
Past	17.7	16.9	17.5	20.5	23.0	1.2	1.0	1.0	1.3	1.6
Current	48.8	49.1	46.8	44.2	44.8	7.0	6.7	5.0	4.9	6.5
Alcohol consumption (%)										
<1 day per week	38.9	33.6	30.3	32.2	35.5	90.7	87.8	86.6	84.6	86.3
⩾1 day per week	61.1	66.4	69.7	67.8	64.5	9.3	12.2	13.4	15.4	13.7
Leisure-time physical activity (%)										
<1 day per month	61.5	58.8	56.9	57.3	62.5	71.4	68.2	65.7	67.5	71.4
1–3 days per month	15.9	17.4	20.5	20.5	18.0	8.7	9.3	11.5	10.4	9.2
⩾1 day per week	22.6	23.9	22.6	22.2	19.5	19.8	22.4	22.8	22.1	19.4
History of hypertension (%)	20.2	20.7	17.4	16.6	17.0	26.7	23.0	19.3	17.0	20.1
History of diabetes mellitus (%)	14.3	10.5	5.5	4.4	4.7	9.0	6.6	2.7	2.2	3.2

Abbreviation: BMI, body mass index. [a]Difference of body weight between baseline and 5-year follow-up survey. [b]The weight change was expressed as percentage: ((weight at the 5-year follow-up survey−weight at baseline)/weight at baseline) × 100.

up survey (at the start of follow-up) according to the weight change between baseline and 5-year survey. Between the two surveys, 61.4% of men and 66% of women had a stable weight (<2.5 kg change). Both men and women who lost weight tended to be older, were less likely to be an alcohol drinker and had a higher BMI at baseline and a history of hypertension and diabetes mellitus. Men who gained weight were more likely to be past smokers, whereas those who lost weight were more likely to be current smokers.

Table 2 shows the hazard ratios of all-cause and cause-specific mortality according to weight change. In both men and women, there was a reverse J-shaped association, with a weight loss of 2.5 kg or more and a weight gain of 5 kg or more being significantly related to an increased risk of all-cause mortality. Multivariate-adjusted hazard ratios (95% CI) of all-cause mortality for weight loss of 5 kg or more versus stable weight were 1.62 (1.45–1.81) in men and 1.76 (1.51–2.05) in women. The corresponding values for weight gain of 5 kg or more were 1.40 (1.22–1.59) and 1.25 (1.02–1.54). After exclusion of deaths in the first 3 years of follow-up, the association with weight loss was attenuated but remained statistically significant in men, whereas there was no material change in women.

Among subjects whose weight was stable (<2.5 kg change) over the 5 years between baseline and the 5-year survey, the multivariate-adjusted hazard ratios (95% CI) of all-cause mortality for increasing BMI levels at the 5-year survey (<19, 19 to <21, 21 to <23, 23 to <25, 25 to <27, 27 to <30 and $\geqslant 30\,kg\,m^{-2}$) were 1.8 (1.4–2.2), 1.3 (1.2–1.6), 1.1 (1.0–1.3), 1.0 (reference), 1.0 (0.8–1.1), 0.7 (0.6–1.0) and 0.9 (0.5–1.6) in men and 2.0 (1.5–2.7), 1.3 (1.0–1.6), 1.4 (1.1–1.7), 1.0 (reference), 1.3 (1.1–1.7), 1.3 (1.0–1.7) and 1.2 (0.7–1.8) in women.

Weight loss was significantly associated with an increased risk of cancer mortality in both men and women (Table 2). Multivariate-adjusted hazard ratios (95% CI) for weight loss of 5 kg or more were 1.78 (1.51–2.10) in men and 1.61 (1.28–2.04) in women. Although the risk was attenuated after exclusion of early deaths, the increased risk of cancer mortality associated with weight loss of 5 kg or more remained statistically significant. Weight gain was not measurably related to cancer mortality. The risk of cardiovascular disease mortality increased in men who lost weight and in women who either lost or gained weight. However, multivariate adjustment and exclusion of early deaths substantially attenuated the association with weight loss, whereas it strengthened the association with weight gain in women. When the analysis was carried out separately for heart disease and cerebrovascular disease, a significant increase in heart disease mortality was observed in men who lost weight by 2.5 kg or more and in women who gained weight by 5 kg or more, whereas cerebrovascular disease mortality did not significantly differ by the levels of weight change in both men and women.

Table 2 Multivariate-adjusted hazard ratios and 95% confidence intervals of deaths according to weight change categories

	Men					*Women*				
	⩾5 kg loss	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*⩾5 kg gain*	*⩾5 kg loss*	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*⩾5 kg gain*
Person-year of follow-up	26 495	27 759	192 947	34 458	30 900	27 839	33 519	256 179	42 588	27 280
All-cause										
No of deaths	421	315	1498	242	281	221	176	842	132	104
Adjusted HR[a]	1.62	1.26	1.00	1.08	1.40	1.76	1.30	1.00	1.11	1.25
95% CI	1.45–1.81	1.12–1.43	Reference	0.94–1.24	1.22–1.59	1.51–2.05	1.10–1.53	Reference	0.92–1.34	1.02–1.54
Adjusted HR[b]	1.43	1.25	1.00	1.13	1.29	1.70	1.19	1.00	1.13	1.31
95% CI	1.25–1.63	1.09–1.44	Reference	0.97–1.32	1.11–1.51	1.42–2.03	0.98–1.45	Reference	0.91–1.39	1.03–1.65
Cancer										
No of deaths	188	126	666	104	110	88	71	425	57	37
Adjusted HR[a]	1.78	1.17	1.00	1.03	1.22	1.61	1.13	1.00	0.89	0.83
95% CI	1.51–2.10	0.97–1.42	Reference	0.84–1.27	0.99–1.50	1.28–2.04	0.88–1.46	Reference	0.67–1.17	0.59–1.18
Adjusted HR[b]	1.53	1.19	1.00	1.12	1.15	1.45	0.98	1.00	0.88	0.82
95% CI	1.25–1.88	0.95–1.48	Reference	0.89–1.40	0.91–1.47	1.11–1.91	0.72–1.32	Reference	0.64–1.20	0.55–1.20
Cardiovascular disease										
No of deaths	79	97	349	58	66	56	47	202	35	32
Adjusted HR[a]	1.25	1.64	1.00	1.10	1.34	1.58	1.32	1.00	1.33	1.66
95% CI	0.97–1.60	1.31–2.05	Reference	0.83–1.46	1.02–1.76	1.17–2.15	0.96–1.81	Reference	0.92–1.90	1.13–2.44
Adjusted HR[b]	1.17	1.64	1.00	1.10	1.07	1.42	1.22	1.00	1.45	1.93
95% CI	0.88–1.57	1.27–2.12	Reference	0.80–1.51	0.76–1.50	0.98–2.07	0.82–1.80	Reference	0.96–2.19	1.25–2.99
Heart disease										
No of deaths	48	57	185	29	33	28	19	86	17	14
Adjusted HR[a]	1.40	1.81	1.00	1.03	1.26	1.60	1.14	1.00	1.62	1.82
95% CI	1.01–1.94	1.34–2.43	Reference	0.70–1.53	0.86–1.84	1.04–2.49	0.69–1.88	Reference	0.96–2.75	1.02–3.25
Adjusted HR[b]	1.45	2.00	1.00	1.07	1.10	1.48	1.04	1.00	1.71	2.14
95% CI	1.00–2.10	1.44–2.80	Reference	0.68–1.69	0.69–1.77	0.86–2.56	0.56–1.95	Reference	0.91–3.20	1.07–4.27
Cerebrovascular disease										
No of deaths	24	29	143	20	27	21	22	99	16	16
Adjusted HR[a]	0.94	1.20	1.00	0.94	1.38	1.38	1.36	1.00	1.13	1.53
95% CI	0.60–1.46	0.80–1.78	Reference	0.58–1.50	0.90–2.11	0.85–2.24	0.85–2.17	Reference	0.67–1.93	0.89–2.64
Adjusted HR[b]	0.83	1.05	1.00	1.09	0.99	1.04	1.22	1.00	1.20	1.66
95% CI	0.49–1.41	0.65–1.70	Reference	0.67–1.78	0.58–1.69	0.56–1.93	0.70–2.13	Reference	0.66–2.17	0.91–3.05

Abbreviations: CI, confidence interval; HR, hazard ratio. [a]Adjusted for age (year), study area (11 areas), body mass index (<21, 21 to <23, 23 to <25, 25 to <27 and ⩾27 kg m^{-2}), smoking (never, past, current with a consumption of <20 or ⩾20 cigarettes per day), alcohol consumption (nondrinker, occasional drinker, drinkers with a consumption of <150, 150–299, 300–449 or ⩾450 g ethanol per week for men and nondrinker, occasional drinker, drinkers with a consumption of <150 or ⩾150 g ethanol per week for women), leisure-time physical activity (<1 time per month, 1–3 times per month, ⩾1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no). [b]Further excluded deaths within the first 3 years of follow-up.

An increased risk of all-cause mortality associated with weight loss of 5 kg or more was observed irrespective of initial BMI, but was pronounced in lean persons (Figure 1). Compared with subjects who had normal weight at baseline (BMI: 18.5–24.9 kg m^{-2}) and experienced a little weight change at the 5-year survey (<2.5 kg), the multivariate-adjusted hazard ratios (95% CI) for underweight subjects who lost weight by 5 kg or more were 2.85 (2.31–3.53) in men and 3.62 (2.65–4.95) in women; for overweight persons; the corresponding hazard ratios were 1.42 (1.18–1.70) in men and 1.82 (1.45–2.28) in women. Weight gain was related to an increased risk of all-cause mortality among underweight subjects but not among normal weight or overweight persons. An increased risk of cancer mortality associated with weight loss was observed irrespective of the initial BMI in both men and women, although the association was pronounced in underweight men (hazard ratio = 2.66, 95% CI: 1.92, 3.68). With regard to cardiovascular disease mortality, the association with weight change did not differ by initial BMI in men, whereas it was more evident among underweight subjects in women.

In men, an increased risk of all-cause, cancer and cardiovascular disease mortality associated with weight loss was observed in both nonsmokers and current smokers but was more pronounced in nonsmokers (Table 3). However, an increase risk of cancer, cardiovascular disease and cerebrovascular disease mortality with weight gain was observed in nonsmokers but not in current smokers. In the analysis by age, an increased risk of cardiovascular disease mortality in relation to weight loss and weight gain was observed in older men only; the association with weight loss reflected an increased risk of coronary heart disease mortality, whereas

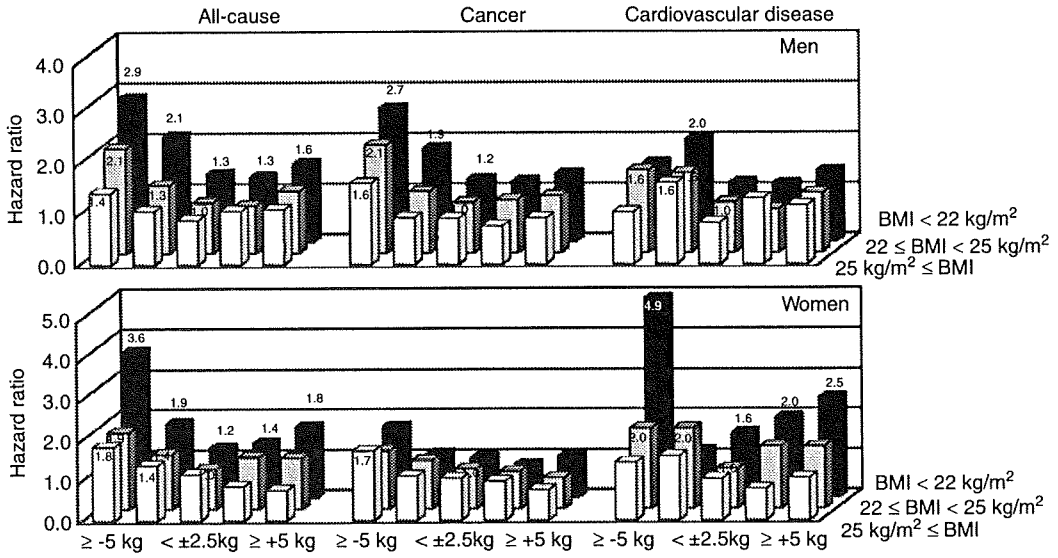

Figure 1 Multivariate-adjusted hazard ratio (a group of individuals with normal weight at baseline and stable weight for 5 years was used as reference. Hazard ratio was adjusted for age (years), study area (11 areas), smoking (never, past, current with a consumption of <20 or ⩾20 cigarettes per day), alcohol consumption (nondrinker, occasional drinker, drinkers with a consumption of <150, 150–299, 300–449 or ⩾450 g ethanol per week for men; and nondrinker, occasional drinker, drinkers with a consumption of <150 or ⩾150 g ethanol per week for women), leisure-time physical activity (<1 time per month, 1–3 times per month, ⩾1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no)) of deaths according to weight change categories and initial body mass index. Abbreviation: BMI, body mass index.

that with weight gain was due to increased mortality of cerebrovascular disease. In contrast, an increased risk of cardiovascular disease mortality with weight change was more evident in the younger age group in women.

Discussion

In this large-scale population-based prospective study in Japanese men and women, the relation between weight change over a 5-year period and all-cause mortality was reverse J-shaped, with both loss and gain in weight of 5 kg or more being related to an increased risk of all-cause mortality. The association was observed irrespective of sex, age, baseline BMI and smoking status and remained significant even after adjustment for covariates. The risk of cancer mortality increased in both men and women who lost weight by 5 kg or more. Weight loss in men and women and weight gain in women were related to an increased risk of cardiovascular disease mortality.

The observed weight loss–mortality association in this study, as well as in many other studies,[10–19] may be accounted for preexisting disease and smoking, factors affecting both body weight and mortality. However, this idea has been supported by only few studies.[20,22] Many other studies found an increased mortality with weight loss even after excluding subjects with preexisting disease[12,13,16–19] or deaths in the early period of follow-up.[13,14,18,19] Similarly, an increased mortality risk among weight losers has been observed with adjustment for smoking status[12,14,17,18] or in nonsmokers.[13,16,19] In the present analytic cohort comprising only persons without serious disease, the association between weight loss and mortality remained statistically significant even after excluding deaths in the first 3 years of follow-up and was observed in both nonsmokers and smokers. Our data argue against the possibility that the weight loss–mortality association is attributed to preexisting disease or smoking.

With regard to weight gain, previous findings are conflicting. In a 1993 review of 11 studies, Andres *et al.*[11] concluded that the risk of overall mortality increased in persons who gained excessive weight, whereas it decreased in those who experienced moderate weight gain. Our finding that an increased mortality risk associated with weight gain of 5 kg or more agrees with the review. In contrast, several recently published studies have shown no association with weight gain.[10,12–15,17,20–22] We have no clear explanation for the discrepancy, but the effect of weight gain on mortality may differ according to sex, age, race, cause of death, period of weight change assessed and period of follow-up.

The association between weight change and mortality may be modified by the initial BMI levels. However, we observed an increased risk of mortality with weight loss even in overweight subjects, a finding compatible with the results of several studies showing increased mortality irrespective of the initial BMI levels.[13,14,16–18,24] We also observed an increased risk of mortality after weight gain even in underweight subjects. Data were limited regarding this point, but in one study,[16] weight gain was related to an

Table 3 Multivariate-adjusted hazard ratios and 95% confidence intervals of deaths according to weight change categories and smoking status or age categories

	Men				*Men*				*Women*			
	Nonsmoker		*Current smoker*		*<60 year*		*≥60 year*		*<60 year*		*≥60 year*	
	HR[a]	*95% CI*	*HR*[a]	*95% CI*	*HR*[b]	*95% CI*	*HR*[b]	*95% CI*	*HR*[b]	*95% CI*	*HR*[b]	*95% CI*
All-cause												
≥5 kg loss	1.76	1.50–2.07	1.50	1.28–1.75	1.68	1.40–2.02	1.58	1.37–1.82	1.87	1.44–2.43	1.68	1.39–2.03
2.5–4.9 kg loss	1.36	1.14–1.63	1.21	1.02–1.43	1.12	0.91–1.40	1.34	1.15–1.55	1.40	1.07–1.84	1.23	1.00–1.51
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	0.96	0.78–1.18	1.20	0.99–1.45	1.16	0.94–1.41	1.02	0.84–1.23	0.93	0.70–1.23	1.26	0.99–1.61
≥5 kg gain	1.56	1.30–1.87	1.25	1.02–1.52	1.27	1.03–1.57	1.49	1.26–1.76	1.29	0.96–1.75	1.14	0.85–1.53
Cancer												
≥5 kg loss	2.13	1.68–2.70	1.48	1.16–1.88	1.92	1.45–2.54	1.69	1.38–2.08	1.60	1.10–2.34	1.64	1.21–2.21
2.5–4.9 kg loss	1.40	1.06–1.83	1.05	0.80–1.37	1.11	0.78–1.56	1.20	0.95–1.51	1.05	0.70–1.58	1.18	0.86–1.63
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	0.86	0.62–1.19	1.22	0.93–1.61	1.16	0.84–1.59	0.95	0.72–1.26	0.72	0.47–1.08	1.07	0.74–1.57
≥5 kg gain	1.39	1.04–1.85	1.05	0.77–1.44	1.21	0.86–1.69	1.23	0.95–1.60	0.88	0.55–1.40	0.76	0.45–1.27
Cardiovascular disease												
≥5 kg loss	1.44	0.99–2.10	1.22	0.87–1.71	1.14	0.74–1.75	1.32	0.97–1.80	1.84	1.04–3.29	1.43	1.00–2.04
2.5–4.9 kg loss	1.96	1.39–2.75	1.46	1.07–1.99	1.04	0.66–1.64	1.98	1.52–2.59	1.37	0.74–2.54	1.27	0.88–1.85
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	1.34	0.90–2.00	0.89	0.59–1.36	1.20	0.80–1.80	1.00	0.67–1.47	1.25	0.70–2.25	1.32	0.83–2.10
≥5 kg gain	1.94	1.34–2.79	0.97	0.63–1.49	1.21	0.79–1.86	1.43	1.00–2.03	1.86	1.02–3.40	1.46	0.88–2.41
Heart disease												
≥5 kg loss	1.77	1.09–2.89	1.33	0.86–2.07	1.14	0.64–2.02	1.56	1.05–2.32	4.07	1.89–8.77	1.09	0.63–1.87
2.5–4.9 kg loss	2.16	1.36–3.45	1.66	1.11–2.48	1.20	0.68–2.13	2.16	1.52–3.08	1.07	0.32–3.61	1.10	0.63–1.91
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	1.21	0.66–2.21	0.88	0.50–1.55	0.94	0.51–1.73	1.12	0.67–1.88	1.77	0.70–4.48	1.49	0.78–2.85
≥5 kg gain	1.56	0.88–2.78	1.14	0.67–1.93	1.52	0.89–2.60	1.05	0.60–1.82	2.10	0.75–5.83	1.63	0.80–3.32
Cerebrovascular disease												
≥5 kg loss	1.25	0.66–2.35	0.76	0.40–1.44	0.92	0.43–1.94	0.95	0.55–1.64	0.43	0.10–1.81	1.70	1.00–2.90
2.5–4.9 kg loss	1.80	1.04–3.12	0.84	0.46–1.55	0.72	0.31–1.67	1.46	0.92–2.32	1.57	0.73–3.39	1.29	0.72–2.31
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	1.24	0.66–2.31	0.76	0.37–1.58	1.28	0.70–2.37	0.59	0.27–1.28	1.15	0.53–2.48	1.05	0.50–2.21
≥5 kg gain	2.05	1.20–3.52	0.87	0.41–1.82	0.74	0.33–1.66	1.85	1.12–3.07	1.50	0.65–3.47	1.46	0.71–2.99

Abbreviations: CI, confidence interval; HR, hazard ratio. [a]Adjusted for age (year), study area (11 areas), body mass index (<21, 21 to <23, 23 to <25, 25 to <27 and ≥27 kg m^{-2}), alcohol consumption (nondrinker, occasional drinker, drinkers with a consumption of <150, 150–299, 300–449 or ≥450 g ethanol per week for men and nondrinker, occasional drinker, drinkers with a consumption of <150 or ≥150 g ethanol per week for women), leisure-time physical activity (<1 time per month, 1–3 times per month, ≥1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no). [b]Further adjusted for smoking (never, past, current with a consumption of <20 or ≥20 cigarettes per day).

increased risk of mortality among both nonoverweight and overweight groups. These findings may suggest that weight loss and gain predict an increased mortality risk irrespective of initial BMI levels.

Limited evidence is available regarding the relation of weight change to risk of cause-specific mortality. Three studies among Western populations have examined overall cancer mortality in association with weight change, but the results are all null.[16,20,21] In our study, however, weight loss was significantly associated with an increased risk of cancer mortality. In our previous report, the risk of cancer mortality significantly increased in underweight subjects,[9] and this association was replicated in the present analysis among subjects with stable weight over a 5-year period. These findings from the JPHC Study indicate that both weight loss and underweight are important predictors of an increased risk of cancer mortality in Japanese. In contrast, we did not observe any association between weight gain and cancer mortality except for nonsmoking men. This finding seems to contradict the established association between obesity and cancer.[25,26] However, several Western studies[16,20,21] have reported no increase in cancer mortality with weight gain. Japanese differ substantially from Western populations not only in the prevalence of obesity but also in the type of major cancers. For example, stomach cancer and esophageal cancer (squamous cell carcinoma), the risks of which have been shown to increase among persons with a low BMI,[26] are much more common in Japan than in Western countries.[27] This could be an explanation why the present finding, especially for weight loss, was not compatible with those derived from Western studies.

Obesity is a known risk factor for cardiovascular disease,[28] and overweight was a significant predictor of cardiovascular disease mortality in the JPHC Study.[9] It may thus be

reasonable to expect that the risk of cardiovascular disease increased with weight gain and decreased with weight loss. However, existing data are not fully compatible with the idea. For instance, some studies[21,22] have reported a suggestion of an increased risk of cardiovascular disease mortality with weight gain, whereas some others[13,14,20] did not detect such an association. In this study, increased mortality of cardiovascular disease with weight gain was observed in women, nonsmoking men and older men. The finding of an increased risk of cardiovascular disease mortality with weight loss in men and younger women is unexpected, although similar findings have been documented in several studies.[13,14,18,20] It is not clear why the association between weight change and cardiovascular disease mortality differed by sex in this study. Given the similarity of the result for nonsmoking men and overall women (Table 3), 95% of whom were nonsmokers (Table 1), we speculate that smoking status may have modified the weight change–mortality association.

There are several plausible mechanisms to explain the association between weight gain and cardiovascular disease mortality. Weight gain increases the risk of diabetes mellitus[29,30] and hypertension,[31] worsens a profile of cardiovascular disease risk factors,[32] and induces inflammation.[33] However, the mechanism for the weight loss–cardiovascular disease association is unclear. Depression may partly account for the link due to its potential effects on both weight and mortality of cardiovascular disease.[34] Moreover, weight loss in the elderly is mainly caused by muscle loss,[35,36] which could deteriorate the risk factors for cardiovascular disease.[37] With regard to cancer, insulin is hypothesized to be involved in the pathogenesis of several cancers through effects on insulin-like growth factors[38] and could link obesity to cancer but this mechanism may be less likely to work in Japanese because of their low ability to secrete insulin.[39] There is biological evidence that supports the observed positive association with weight loss. A biomarker study showed that weight loss was associated with increased oxidative DNA damage,[40] which is hypothesized to have a major role in carcinogenesis.[41] In addition, weight loss may increase the risk of cancer because of its adverse effects on immune function.[42]

As large weight loss is one clinical condition of frailty,[43] the observed weight loss–mortality association could be explained in this context. Frailty is a state of increased vulnerability to stressors resulting from decreased physiological reserves and dysregulation of multiple physiological systems, and limited capacity to maintain homeostasis and to respond to internal and external stresses.[44] In fact, an increased risk associated with frailty was observed for various health outcomes, including falls, disability, hospitalization and mortality.[43] Although frailty itself may not be a direct cause of early death, deterioration of organ systems resulting from frailty could increase mortality risk.[45] Some studies have shown that frail persons, compared with nonfrail persons, had higher levels of markers of inflammation,[43] a condition that has been linked to cancer and cardiovascular disease.[46,47]

The strengths of this study are large sample size, population-based prospective design and few subjects being lost to follow-up (0.6%). Death registration in Japan, which we used to identify the cause of death, is believed to be complete. Moreover, we excluded subjects with serious disease and adjusted for or stratified by important confounding variables. To minimize the effect of potential occult disease, analysis was also carried out with further exclusion of deaths occurring in the first 3 years of follow-up. This study also had some limitations. First, we had no information about whether weight loss is intentional or unintentional. Intentional weight loss has been related to lower mortality, whereas unintentional weight loss has been related to higher mortality.[48,49] If we could exclude subjects with intentional weight loss, the association between weight loss and mortality would become stronger. Second, as we did not measure body composition, we did not know whether weight loss represented fat loss or muscle loss. However, it may not be feasible to measure body composition in a large sample. Third, although we extensively excluded subjects who reported serious diseases and deaths in the first 3 years of follow-up and adjusted for covariates including BMI at baseline and smoking status, we cannot completely rule out the possibility of occult disease and bias due to residual confounding. Fourth, we used self-reported weight and height. However, we confirmed that the self-reported BMI was highly correlated with the measured one. Finally, the present finding for weight loss should not be applied to clinical settings in which obese patients are instructed to decrease weight by health professionals.

Obesity and weight gain have been increasingly recognized as a major health issue,[1] but less attention has been paid to the adverse health outcome associated with underweight and weight loss except for populations that are subject to malnutrition. In the present finding among Japanese, who are on an average much thinner than Westerners, large weight change, either gain or loss, predicted subsequent mortality risk, with weight loss conferring greater risk than weight gain. More research is required to clarify the impact of intentional weight loss on subsequent morbidity and mortality and elucidate the mechanisms linking weight change and mortality risk.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank Drs Yumi Matsushita, Kyoko Kirii (both International Medical Center of Japan) and Masayuki Kato (Japan

Foundation for the Promotion of International Medical Research Cooperation) for their helpful discussions. This work was supported by Grants-in-Aid for Cancer Research (19shi-2) and a Health Sciences Research Grant (Research on Comprehensive Research on Cardiovascular Diseases H19-016) from the Ministry of Health, Labour and Welfare of Japan.

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Appendix

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The Journal of Nutrition
Nutritional Epidemiology

Soy Product and Isoflavone Intakes Are Associated with a Lower Risk of Type 2 Diabetes in Overweight Japanese Women[1,2]

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Abstract

Isoflavones have been shown to improve glucose metabolism, but epidemiologic data are limited. We prospectively investigated the relationship between soy product and isoflavone intake and the risk of developing type 2 diabetes among Japanese adults. Participants were 25,872 men and 33,919 women aged 45–75 y, who participated in the second survey of the Japan Public Health Center-Based Prospective Study and had no history of diabetes. Soy product and isoflavone intakes were ascertained using a 147-item FFQ. Odds ratios of self-reported, physician-diagnosed type 2 diabetes over 5 y were estimated using logistic regression analysis. A total of 1114 new cases of type 2 diabetes were self-reported. Intakes of soy products and isoflavones were not significantly associated with type 2 diabetes in either men or all women. However, among overweight women (BMI ≥25 kg/m^2), a higher intake of soy products was associated with a lower risk of type 2 diabetes; multivariable-adjusted odds ratios (95% CI) for the lowest through highest quintiles of soy product intake were 1.00 (reference), 0.78 (0.62–1.18), 0.79 (0.52–1.20), 0.62 (0.39–0.99), and 0.89 (0.55–1.44), respectively, and we found a similar risk pattern for daidzein and genistein intakes. Overall, our results suggest that there are no benefits of soy product or isoflavone intake with respect to risk of type 2 diabetes in either men or women. The possible protective associations of soy and isoflavone intakes among overweight women deserves further investigation. J. Nutr. 140: 580–586, 2010.

Introduction

The prevalence of type 2 diabetes is increasing worldwide (1) and is now relatively high among the Japanese, who have experienced rapid economic growth over the past several decades (2). Reports have suggested that soybeans and soy products such as tofu and *natto* (fermented soybeans), foods commonly consumed by the Japanese, may have beneficial effects on health (3). Animal studies have found that isoflavones, a major phytoestrogen found in these foods, improve glucose tolerance and exert an antidiabetic effect (4), suggesting that soy product and isoflavone intake may decrease risk of type 2 diabetes. However, human data on this issue are limited.

Of 2 cross-sectional studies that examined the association between isoflavone intake and glucose tolerance, 1 reported lower levels of fasting and postchallenge insulin concentrations among persons with high isoflavone intake than among those with low intake (5), whereas another found no link between isoflavone intake and glycated hemoglobin or fasting insulin (6). In prospective studies, elevated intake of soybeans and other legumes has been linked to a decreased risk of glucose intolerance (7,8) and type 2 diabetes (9); however, the association with isoflavone intake was not assessed in these reports. Some (10,11), but not all (12–14), intervention studies of patients with type 2 diabetes have reported favorable effects of isoflavones and soy-based meal on glycated hemoglobin or insulin resistance.

Here, to assess the association of soy products and isoflavones with the development of type 2 diabetes, we prospectively investigated the relationship of dietary intake of soy products and isoflavones (genistein and daidzein) with the risk of developing type 2 diabetes using data from a large-scale, population-based cohort study in Japan.

Participants and methods

Study population. The Japan Public Health Center-Based Prospective (JPHC) Study was launched in 1990 for cohort I and in 1993 for cohort II

[1] Supported by Grants-in-Aid for Cancer Research (19shi-2) and a Health Sciences Research Grant (Research on Comprehensive Research on Cardiovascular Diseases H19-016) from the Ministry of Health, Labour and Welfare of Japan.
[2] Author disclosures: A. Nanri, T. Mizoue, Y. Takahashi, K. Kirii, M. Inoue, M. Noda, and S. Tsugane, no conflicts of interest.
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0022-3166/08 $8.00

Manuscript received September 14, 2009. Initial review completed October 20, 2009. Revision accepted December 6, 2009.
First published online January 6, 2010; doi:10.3945/jn.109.116020.

(15). Participants were residents of 11 public health centers aged 40–69 y (assessed at each baseline survey). Our study was approved by the Institutional Review Board of the National Cancer Center of Japan.

Among the study population at baseline (n = 140,420), we excluded those who resided in 2 public center areas because of the differences in recruitment criteria. Of the remaining 116,672 eligible participants, 95,373 (81.7%) responded to the questionnaire survey at the baseline. Of these, 80,128 (84.0%) also responded to the 5-y survey (second survey), which is the baseline of the present analysis. Of these, 71,075 (88.7%) responded to the 10-y survey (third survey). We excluded participants who reported a history of type 2 diabetes (n = 5183) or severe diseases (n = 6284), including cancer, cerebrovascular disease, myocardial infarction, chronic liver disease, and renal disease, at baseline or second surveys. An additional 590 participants who reported extreme total energy intake (outside of mean ± 3 SD, according to sex) were excluded, leaving a total of 59,791 participants (25,872 men and 33,919 women) ultimately enrolled in our analysis.

Soy product and isoflavone intake. At baseline, second, and third surveys, participants completed a self-administered questionnaire that included queries regarding height, body weight, medical history, smoking habit, alcohol consumption, physical activity, diet, and other lifestyle factors. In the present analysis, we used data from the second survey, which was conducted in 1995 for cohort I and in 1998 for cohort II, as baseline. We did this because the questionnaire used for that survey contained more comprehensive information on food intake than that used for the baseline survey. At the second survey, a FFQ was used to assess intakes of 147 food and beverage items over the past year (16). *Miso* (fermented soybean paste) soup, tofu, *yushidofu* (predrained tofu), *koyadofu* (freeze-dried tofu), *aburaage* (deep-fried tofu), *natto* (fermented soybeans), and soy milk were included in the FFQ as soy products. For *miso* soup, potential responses regarding intake frequency were: almost never, 1–3 d/mo, 1–2 d/wk, 3–4 d/wk, 5–6 d/wk, or daily. Potential responses to the number of bowls consumed were: <1, 1, 2, 3, 4, 5, 6, 7–9, or ≥10/d. For items other than *miso* soup and soy milk, participants described consumption frequency by choosing 1 of 9 options (almost none, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, once/d, 2–3 times/d, 4–6 times/d, or ≥7 times/d). A standard portion size was specified for each food and respondents were asked to choose their usual portion size among 3 options (less than one-half of the standard portion size, standard portion size, or >1.5 times of the standard portion size). Nine frequency options were given for soy milk: almost none, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 cup (1 cup = 200 mL)/d, 2–3 cups/d, 4–6 cups/d, 7–9 cups/d, or ≥10 cups/d. Total soy product consumption was calculated from these responses, and total isoflavones (daidzein and genistein) intake was calculated based on a food composition table specifically developed to assess isoflavone content in Japanese foods (17,18).Validity was assessed among subsamples using either 14- or 28-d dietary records. Spearman correlation coefficients between energy-adjusted intake for soy products, daidzein, and genistein derived from the FFQ and that derived from the dietary records were 0.44–0.60 for cohorts I and II (19–21). The corresponding values for daidzein and genistein between energy-adjusted intake derived from the FFQ and serum concentration was 0.26 and 0.22, respectively, whereas that between energy-adjusted intake derived from the FFQ and creatinine-adjusted urinary excretion was 0.40 and 0.30, respectively (21). With regard to the reproducibility of estimations between the 2 FFQ administered 1 y apart, Spearman correlation coefficients for energy-adjusted intake of soy products, daidzein, and genistein were 0.41–0.67 for cohorts I and II (19,21,22).

Ascertainment of type 2 diabetes. Type 2 diabetes newly diagnosed during the 5-y period after the second survey was determined by a self-administered questionnaire at the third survey. At the third survey, study participants were asked if they had ever been diagnosed with diabetes and, if so, when the initial diagnosis had been made. Because we used the second survey as the starting point of observation for the incidence of type 2 diabetes, only patients who were diagnosed after 1995 for cohort I and 1998 for cohort II were regarded as incident cases during follow-up. Details regarding assessment of the validity of self-reported diabetes have been described elsewhere (23). In a previous study we conducted, 94% of self-reported diabetes cases were confirmed as such by medical records. On application of these data to the survey results obtained from a JPHC subpopulation (health checkup participants) whose plasma glucose data were available, the sensitivity and specificity of self-reported diabetes were estimated to be 82.6 and 99.7%, respectively.

Statistical analysis. Soy product, daidzein, and genistein intakes were adjusted for total energy intake using a residual method. Participants were divided by gender into intake quintiles. Confounding variables considered were as follows: age (year, continuous), study area (9 areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27 kg/m^2), smoking habit (lifetime nonsmoker, former smoker, or current smoker with a consumption of either <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/d for men and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/d for women), leisure-time physical activity (<once/mo, 1–3 times/mo, or ≥once/wk), history of hypertension (yes or no), family history of diabetes mellitus (yes or no), coffee consumption (almost never, <1 cup/d, 1 cup/d, or ≥2 cups/d), green tea consumption (almost never, <1 cup/d, 1 cup/d, 2–3 cups/d, or ≥4 cups/d), energy-adjusted magnesium intake (mg/d, continuous), energy-adjusted calcium intake (mg/d, continuous), energy-adjusted fiber intake (g/d, continuous), energy-adjusted vegetable intake (g/d, continuous), energy-adjusted fish intake (g/d, continuous), and total energy intake (kJ/d, continuous). An indicator variable for missing data was created for each covariate. We confirmed that the results were unchanged when analyses were conducted among participants with no missing information of all covariates. Trends of differences in proportions and means of confounding factors according to quintile categories of soy product intake were statistically tested using the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, with ordinal numbers 0–4 assigned to the quintile categories of soy product intake.

Odds ratios and 95% CI of type 2 diabetes for the quintiles of soy product, daidzein, and genistein intakes were estimated using multiple logistic regression analysis, taking the lowest quintile category as reference. The first model was adjusted for age and study area, and the multivariable model was further adjusted for BMI, smoking habit, alcohol consumption, leisure-time physical activity, history of hypertension, family history of diabetes, coffee consumption, green tea consumption, magnesium intake, calcium intake, fiber intake, vegetable intake, fish intake, and total energy intake. We also analyzed data by BMI (<25 kg/m^2 or ≥25 kg/m^2), smoking status (nonsmoker or current smoker) in men only, and menopausal status (premenopausal or postmenopausal) in women only. The cutoff for BMI used in this study was the lower limit of obesity for Japanese populations, which was determined by the Japan Society for the Study of Obesity (24). Because most women (95.8%) were nonsmokers, we did not perform analysis stratified by smoking status among women. The significance of the interactions between soy product, daidzein, and genistein intakes and stratifying variables was assessed by the Wald chi-squared statistic. Two-sided P-values <0.05 were considered significant. All analyses were performed using SAS version 9.1 (SAS Institute).

Results

We identified 1114 new cases (634 men and 480 women) of self-reported type 2 diabetes over the 5-y period between the second and third surveys. At the time of the second survey (the baseline of the present analysis), both men and women with incident type 2 diabetes had a higher BMI and were more likely to report a family history of diabetes mellitus and own history of hypertension than those without (Table 1). Women with incident type 2 diabetes were also more likely to be older and physically inactive during leisure time and consumed less coffee than those without type 2 diabetes.

TABLE 1 Baseline characteristics according to participants with and without incident type 2 diabetes during follow-up in the JPHC Study[1,2]

	Men			Women		
	Nondiabetics	Diabetics	*P*-value[3]	Nondiabetics	Diabetics	*P*-value[3]
Participants, *n*	25,238	634		33,439	480	
Age, *y*	56.6 ± 7.7	56.9 ± 7.3	0.29	57.1 ± 7.8	58.3 ± 7.7	0.001
BMI, *kg/m²*	23.5 ± 2.8	25.2 ± 3.3	<0.001	23.5 ± 3.1	25.7 ± 3.7	<0.001
Current smoker, %	46.5	48.9	0.26	4.2	5.9	0.08
Alcohol consumption ≥1 d/wk, %	68.3	67.3	0.59	11.1	7.5	0.02
Leisure-time physical activity ≥1 d/wk, %	21.0	22.5	0.37	20.3	16.6	0.052
Family history of diabetes mellitus, %	7.7	14.7	<0.001	8.1	14.6	<0.001
History of hypertension, %	17.1	24.8	<0.001	19.0	35.0	<0.001
Coffee consumption ≥1 cup/d,[4] %	32.0	30.8	0.51	35.0	29.3	0.01
Green tea consumption ≥1 cup/d,[4] %	60.3	59.8	0.83	62.1	59.3	0.22
Total energy intake, *KJ/d*	9408 ± 3147	9216 ± 3111	0.13	8019 ± 2787	7959 ± 3023	0.64
Soy products,[5] *g/d*	88 ± 76	90 ± 71	0.43	88 ± 76	94 ± 82	0.09
Miso soup, *mL/d*	261 ± 175	271 ± 175	0.16	215 ± 151	212 ± 157	0.64
Daidzein, *mg/d*	16.0 ± 11.2	16.1 ± 11.3	0.76	15.8 ± 11.0	16.4 ± 12.5	0.21
Genistein, *mg/d*	25.6 ± 18.9	25.9 ± 18.9	0.73	25.5 ± 18.6	26.7 ± 20.9	0.18
Magnesium, *mg/d*	279 ± 56	278 ± 56	0.54	271 ± 50	273 ± 53	0.50
Calcium, *mg/d*	498 ± 223	497 ± 228	0.88	540 ± 211	524 ± 203	0.09
Vegetables, *g/d*	198 ± 120	193 ± 122	0.38	230 ± 134	238 ± 155	0.32
Fiber, *g/d*	11.6 ± 4.5	11.4 ± 4.4	0.33	13.2 ± 4.4	13.5 ± 4.6	0.22
Fish, *g/d*	91 ± 58	89 ± 52	0.46	86 ± 50	87 ± 52	0.61

[1] Values are mean ± SD or percent.
[2] Diagnosis of type 2 diabetes was based on self-report.
[3] Based on *t* test for continuous variables and chi-square test for categorical variables.
[4] 1 cup = 120 mL.
[5] Soy products include *miso* soup, tofu, *yushidofu*, *koyadofu*, *aburaage*, *natto*, and soy milk.

Among both men and women, participants with a relatively higher intake of soy products were older and physically more active in their leisure time and were less likely to be smokers (Table 2). These individuals also had a higher BMI and consumed more magnesium and calcium but less alcohol and coffee and were more likely to report a history of hypertension than participants with lower soy intakes. Women with higher intakes of soy products were less likely to have a family history of diabetes mellitus. Both men and women with high intakes of soy products reported lower total energy intake than those with low soy product intake.

Overall, there were no measurable associations between soy product, daidzein, and genistein intakes and type 2 diabetes in either men or women, although we found somewhat lower odds ratios among women in the higher intake categories (Table 3). In an analysis stratified by BMI, elevated intakes of soy products, daidzein, and genistein were associated with decreased incidence of type 2 diabetes in overweight women (BMI ≥25 kg/m²) (Table 4). Further, risk was significantly decreased in the 4th, but not the highest, quintile of energy-adjusted intakes of soy products, daidzein, and genistein compared with the lowest quintile. The multivariable-adjusted odds ratios (95% CI) of type 2 diabetes for the second through highest quintiles of energy-adjusted intake of soy product versus the lowest quintile were 0.78 (0.52–1.18), 0.79 (0.52–1.20), 0.62 (0.39–0.99), and 0.89 (0.55–1.44), respectively. Similarly, overweight women in the 4th quintile of energy-adjusted intakes of genistein and daidzein had an ~40% lower risk of developing type 2 diabetes than those in the lowest quintile. In the analysis by menopausal status, postmenopausal women in the 4th quintile of energy-adjusted intakes of genistein and daidzein had an ~30% lower risk of type 2 diabetes compared with those in the lowest quintile (genistein: OR 0.73, 95% CI, 0.51–1.05; daidzein: OR 0.69, 95% CI, 0.48–1.00), although the trend association was not clear (genistein: *P*-trend = 0.67; daidzein: *P*-trend = 0.49) (data not shown). Such decreases in odds ratios were not observed in women with a BMI <25 kg/m² or in premenopausal women. The *P*-values for the interactions between soy products, daidzein, and genistein and BMI were 0.33, 0.03, and 0.02, respectively, and those between soy products, daidzein, and genistein and menopausal status were 0.36, 0.08, and 0.17, respectively.

To confirm the results suggestive of a protective association in subgroups of women, we repeated the analysis by creating quintiles based on crude dietary intakes instead of energy-adjusted ones (Table 4). In women with a BMI ≥ 25 kg/m², we observed inverse associations for crude intakes of soy products (*P*-trend = 0.027), daidzein (*P*-trend = 0.042), and genistein (*P*-trend = 0.052). The multivariable-adjusted odds ratio of type 2 diabetes was ~40–50% lower in the highest quintile of crude intakes of soy product, daidzein, and genistein than in the lowest. Such a monotonic decreasing trend was also observed among postmenopausal women, with the odds ratio of type 2 diabetes being 30–40% lower in the highest versus lowest quintiles (data not shown).

In men, there was no measurable association between soy product and isoflavone intakes and risk of type 2 diabetes in any subgroup stratified by BMI or smoking status; the multivariable-adjusted odds ratios of type 2 diabetes for the highest versus the lowest quintile of energy-adjusted intake of soy products were 1.19 (95% CI, 0.77–1.83; *P*-trend = 0.42) in nonoverweight persons, 0.83 (95% CI, 0.53–1.29; *P*-trend = 0.28) in overweight persons, 1.15 (95% CI, 0.76–1.76; *P*-trend = 0.62) in nonsmokers, and 0.87 (95% CI, 0.55–1.39; *P*-trend = 0.62) in smokers (data not shown).

TABLE 2 Baseline characteristics according to quintile categories of soy product intake in the JPHC Study[1–3]

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	*P*-trend[4]
Men, *n* = 25,872						
Participants, *n*	5,174	5,175	5,174	5,175	5,174	
Age, *y*	55.6 ± 7.9	56.1 ± 7.8	56.5 ± 7.7	57.0 ± 7.5	57.8 ± 7.6	<0.001
BMI, *kg/m²*	23.5 ± 2.9	23.4 ± 2.8	23.5 ± 2.8	23.6 ± 2.8	23.8 ± 2.8	<0.001
Current smoker, %	51.6	50.1	48.9	44.4	39.8	<0.001
Alcohol consumption ≥1 d/wk, %	68.3	70.8	69.4	68.7	63.8	<0.001
Leisure-time physical activity ≥1 d/wk, %	18.6	19.8	21.0	21.4	24.6	<0.001
Family history of diabetes mellitus, %	7.5	7.7	8.5	8.0	7.7	0.56
History of hypertension, %	14.1	16.5	16.9	19.1	20.0	<0.001
Coffee consumption ≥1 cup/d,[5] %	41.0	33.8	30.3	28.3	26.8	<0.001
Green tea consumption ≥1 cup/d,[5] %	53.2	61.0	64.2	61.9	60.7	<0.001
Total energy intake, *kJ/d*	9446 ± 3379	9482 ± 3038	9508 ± 3035	9425 ± 2975	9159 ± 3272	<0.001
Soy products, *g/d*	29 ± 10	53 ± 6	73 ± 6	99 ± 10	186 ± 117	<0.001
Miso soup, *mL/d*	130 ± 102	238 ± 134	292 ± 159	315 ± 179	331 ± 204	<0.001
Daidzein, *mg/d*	5.7 ± 2.4	10.5 ± 2.5	14.6 ± 3.6	19.4 ± 5.3	29.9 ± 15.4	<0.001
Genistein, *mg/d*	8.8 ± 3.7	16.4 ± 4.0	22.9 ± 5.7	30.8 ± 8.3	49.4 ± 26.2	<0.001
Magnesium, *mg/d*	242 ± 49	262 ± 44	278 ± 46	292 ± 46	321 ± 60	<0.001
Calcium, *mg/d*	434 ± 253	460 ± 208	488 ± 204	517 ± 194	592 ± 216	<0.001
Vegetables, *g/d*	163 ± 133	188 ± 120	200 ± 122	208 ± 120	228 ± 141	<0.001
Fiber, *g/d*	9.2 ± 4.2	10.7 ± 3.8	11.7 ± 3.9	12.6 ± 4.0	13.8 ± 4.9	<0.001
Fish, *g/d*	84 ± 59	89 ± 51	93 ± 53	95 ± 56	93 ± 60	<0.001
Women, *n* = 33,919						
Participants, *n*	6,783	6,784	6,784	6,784	6,784	
Age, *y*	56.5 ± 8.4	56.8 ± 7.9	56.9 ± 7.7	57.3 ± 7.5	58.1 ± 7.3	<0.001
BMI, *kg/m²*	23.4 ± 3.1	23.4 ± 3.0	23.5 ± 3.1	23.6 ± 3.1	23.9 ± 3.2	<0.001
Current smoker, %	6.5	4.2	3.8	3.4	3.5	<0.001
Alcohol consumption ≥1 d/wk, %	12.9	12.1	12.0	9.7	8.6	<0.001
Leisure-time physical activity ≥1 d/wk, %	18.7	19.5	20.0	20.8	22.1	<0.001
Family history of diabetes mellitus, %	8.9	8.5	8.4	7.5	7.7	0.002
History of hypertension, %	16.3	18.8	18.4	19.4	23.3	<0.001
Coffee consumption ≥1 cup/d,[5] %	46.3	37.2	33.5	30.0	28.0	<0.001
Green tea consumption ≥1 cup/d,[5] %	58.4	64.4	65.3	63.5	58.3	0.45
Total energy intake, *kJ/d*	7989 ± 3058	8164 ± 2803	8139 ± 2664	8000 ± 2565	7800 ± 2823	<0.001
Soy products, *g/d*	29 ± 10	52 ± 5	72 ± 6	97 ± 9	190 ± 117	<0.001
Miso soup, *mL/d*	113 ± 91	192 ± 120	234 ± 140	262 ± 155	276 ± 176	<0.001
Daidzein, *mg/d*	5.6 ± 2.3	10.4 ± 2.6	14.4 ± 3.8	18.9 ± 5.2	29.6 ± 14.8	<0.001
Genistein, *mg/d*	8.8 ± 3.7	16.3 ± 4.1	22.9 ± 5.8	30.4 ± 8.1	49.4 ± 25.3	<0.001
Magnesium, *mg/d*	237 ± 43	258 ± 41	270 ± 39	282 ± 41	309 ± 56	<0.001
Calcium, *mg/d*	486 ± 245	517 ± 207	530 ± 190	552 ± 183	615 ± 203	<0.001
Vegetables, *g/d*	199 ± 133	222 ± 127	233 ± 126	239 ± 126	259 ± 152	<0.001
Fiber, *g/d*	11.1 ± 4.1	12.6 ± 3.8	13.3 ± 3.8	14.0 ± 4.0	15.1 ± 5.0	<0.001
Fish, *g/d*	82 ± 58	86 ± 47	88 ± 46	89 ± 47	86 ± 53	<0.001

[1] Values are mean ± SD or percent.
[2] Soy products include *miso* soup, tofu, *yushidofu*, *koyedofu*, *aburaage*, *natto*, and soy milk.
[3] Quintiles of soy product intake: men, Q1: <43.1 g, Q2: 43.1 to <62.5 g, Q3: 62.5 to <83.7 g, Q4: 83.7 to <117.3 g, Q5: ≥117.3 g; women, Q1: <42.8 g, Q2: 42.8 to <61.7 g, Q3: 61.7 to <82.8 g, Q4: 82.8 to <116.0 g, Q5: ≥116.0 g.
[4] Based on the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, assigning ordinal numbers 0–4 to quintile categories of soy product intake.
[5] 1 cup = 120 mL.

Discussion

In this large-scale, population-based prospective study among Japanese adults, soy product and isoflavone intakes overall were not found to be significantly associated with risk of developing type 2 diabetes in either men or women. In stratified analyses by BMI or menopausal status (women only), however, we found a decrease in risk of type 2 diabetes associated with higher levels of soy product, daidzein, and genistein intakes in overweight women and, to a lesser extent, in postmenopausal women. To our knowledge, ours is the first prospective study to examine the association of isoflavone intakes with type 2 diabetes in an apparently healthy population.

With regard to findings in women, although intake of soy products or isoflavones was not associated with risk of type 2 diabetes for all women in the present study, a suggestive protective association was noted among overweight women. No previous study to our knowledge has assessed the association between intake of these food factors and type 2 diabetes or glucose intolerance stratified by BMI. Among studies

TABLE 3 Odds ratios and 95% CI of type 2 diabetes according to quintile categories of soy product, daidzein, and genistein intakes in the JPHC Study[1]

	Men, n = 26,872					Women, n = 33,919				
	Range of intake	Participants, n	Cases, n	Age- and area-adjusted OR (95% CI)	Multivariable-adjusted[2] OR (95% CI)	Range of intake	Participants, n	Cases, n	Age- and area-adjusted OR (95% CI)	Multivariable-adjusted[2] OR (95% CI)
Soy products										
Q1 (low)	<43.1 g	5174	124	1.00 (reference)	1.00 (reference)	<42.8 g	6783	103	1.00 (reference)	1.00 (reference)
Q2	43.1, <62.5	5175	129	1.05 (0.81, 1.35)	1.05 (0.82, 1.38)	42.8, <61.7	6784	85	0.82 (0.62, 1.10)	0.84 (0.62, 1.13)
Q3	62.5, <83.7	5174	123	1.00 (0.77, 1.29)	1.00 (0.78, 1.30)	61.7, <82.8	6784	97	0.94 (0.70, 1.25)	0.93 (0.69, 1.25)
Q4	83.7, <117.3	5175	125	1.01 (0.78, 1.31)	1.00 (0.76, 1.32)	82.8, <116.0	6784	82	0.78 (0.57, 1.05)	0.77 (0.55, 1.06)
Q5 (high)	≥117.3	5174	133	1.08 (0.82, 1.38)	1.02 (0.75, 1.38)	≥116.0	6784	113	1.05 (0.79, 1.40)	0.98 (0.70, 1.39)
P-trend[3]				0.78	0.95				0.86	0.73
Daidzein										
Q1 (low)	<7.9 mg	5174	119	1.00 (reference)	1.00 (reference)	<7.7 mg	6783	107	1.00 (reference)	1.00 (reference)
Q2	7.9, <11.8	5175	132	1.13 (0.88, 1.46)	1.12 (0.86, 1.45)	7.7, <11.5	6784	83	0.78 (0.58, 1.05)	0.78 (0.58, 1.05)
Q3	11.8, <16.0	5174	140	1.21 (0.94, 1.56)	1.20 (0.92, 1.56)	11.5, <15.8	6784	95	0.90 (0.67, 1.20)	0.92 (0.68, 1.24)
Q4	16.0, <22.4	5175	119	1.03 (0.78, 1.35)	1.00 (0.75, 1.34)	15.8, <22.0	6784	87	0.81 (0.60, 1.10)	0.79 (0.57, 1.09)
Q5 (high)	≥22.4	5174	124	1.08 (0.82, 1.42)	1.01 (0.72, 1.40)	≥22.0	6784	108	1.00 (0.75, 1.34)	0.92 (0.64, 1.32)
P-trend[3]				0.88	0.81				0.88	0.66
Genistein										
Q1 (low)	<12.3 mg	5174	122	1.00 (reference)	1.00 (reference)	<12.2 mg	6783	110	1.00 (reference)	1.00 (reference)
Q2	12.3, <18.4	5175	128	1.06 (0.82, 1.37)	1.05 (0.82, 1.36)	12.2, <18.4	6784	77	0.70 (0.52, 0.95)	0.71 (0.52–0.96)
Q3	18.4, <25.3	5174	140	1.18 (0.91, 1.52)	1.16 (0.91, 1.51)	18.4, <25.3	6784	94	0.86 (0.65, 1.15)	0.88 (0.65, 1.19)
Q4	25.3, <36.0	5175	122	1.03 (0.78, 1.34)	1.00 (0.78, 1.33)	25.3, <35.8	6784	91	0.83 (0.62, 1.11)	0.81 (0.59, 1.11)
Q5 (high)	≥36.0	5174	122	1.03 (0.79, 1.35)	0.96 (0.77, 1.32)	≥35.8	6784	108	0.97 (0.73, 1.29)	0.90 (0.63, 1.29)
P-trend[3]				0.98	0.71				0.79	0.77

[1] Diagnosis of type 2 diabetes were based on self-report.

[2] Adjusted for age (y, continuous), study area (9 areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27 kg/m^2), smoking habit (never, past, current with a consumption of <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men; and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), leisure time physical activity (<once/mo, 1–3 times/mo, or ≥once/wk), history of hypertension (yes or no), coffee consumption (almost never, <1 cup/d, 1 cup/d, or ≥2 cups/d), green tea consumption (almost never, <1 cup/d, 1 cup/d, 2–3 cups/d, or ≥4 cups/d), magnesium intake (mg/d, continuous), calcium intake (mg/d, continuous), vegetable intake (g/d, continuous), fiber intake (g/d, continuous), fish intake (g/d, continuous), and total energy intake (kJ/d, continuous).

[3] Based on multiple logistic regression analysis, assigning ordinal numbers 0–4 to the quintile categories of soy product, daidzein, or genistein intakes.

demonstrating a protective association, most have been conducted among Western populations (5,7,8), whose obesity level is much higher than that among the Japanese. Given that obesity induces insulin resistance (25), soy products and isoflavones may reduce risk of type 2 diabetes by improving insulin sensitivity. Further, a decreased risk of type 2 diabetes associated with high isoflavone intake may be due to the potential favorable effects that isoflavones have on weight control (26,27). In the present study, however, women with an elevated intake of soy products tended to weigh more than those with a decreased intake at baseline (Table 2), and thus the weight reduction pathway does not explain the observed association.

We obtained data suggesting an inverse association between isoflavone intake, especially its crude intake, and risk of type 2 diabetes among postmenopausal but not premenopausal women. Such a differential association by menopausal status has not been documented before. In several previous studies showing a protective association between legume or isoflavone intakes and type 2 diabetes or glucose intolerance, the participants were all postmenopausal women (5,7) or relatively older women [age range: 40–70 y (9)]. Data on premenopausal women, however, are sparse (28). Risk of type 2 diabetes increases after menopause and hormone replacement therapy is known to be related to a decreased risk of type 2 diabetes (29), suggesting a protective role of estrogen in glucose metabolism. In addition, phytoestrogens have been hypothesized to act as estrogen agonists in the low-estrogen milieu after menopause (30). The inverse association among postmenopausal women in the present study may thus be ascribed at least in part to weak estrogenic effects of isoflavones.

The inverse associations we observed among overweight or postmenopausal women became more pronounced when crude intake, rather than an energy-adjusted value using the residual method, was used to create quintiles of dietary exposure. This may suggest that absolute intake of soy food is etiologically more relevant than energy-adjusted intake. However, other explanations are also possible; for instance, energy adjustment may have attenuated the association if those at an elevated risk of developing diabetes tended to decrease energy intake while maintaining soy food intake. Alternatively, the difference may simply be due to a random variation, given that the CI overlapped with each other considerably. The reason behind this discrepancy between the 2 analytical procedures should be identified before any inference regarding a dose-response relationship is made.

We observed no association between intake of soy products and isoflavones and risk of developing type 2 diabetes in overall men or in any subgroup of men. Previously, 2 studies explored the association between these intakes and glucose intolerance in men, but the results were inconsistent (6,8). The etiology of type 2 diabetes may be sex specific, as endogenous sex hormones differentially modulate glycemic status and risk of type 2 diabetes in men and women (31). Our finding indicates that

TABLE 4 Multivariable-adjusted odds ratios and 95% CI of type 2 diabetes according to quintile categories of soy product, daidzein, and genistein intakes by BMI in women of the JPHC Study[1,2]

	BMI <25 kg/m², *n* = 23,586			BMI ≥25 kg/m², *n* = 9459					
	Quintile of energy-adjusted intake			Quintile of crude intake			Quintile of energy-adjusted intake		
	Participants, *n*	Cases, *n*	OR (95% CI)	Participants, *n*	Cases, *n*	OR (95% CI)	Participants, *n*	Cases, *n*	OR (95% CI)
Soy products									
Q1 (low)	4756	46	1.00 (reference)	1797	60	1.00 (reference)	1784	55	1.00 (reference)
Q2	4900	39	0.82 (0.53, 1.28)	1772	42	0.65 (0.43, 0.99)	1730	44	0.78 (0.52, 1.18)
Q3	4796	50	1.05 (0.69, 1.61)	1885	42	0.56 (0.36, 0.87)	1864	47	0.79 (0.52, 1.20)
Q4	4666	38	0.82 (0.51, 1.32)	1908	54	0.67 (0.43, 1.05)	1957	40	0.62 (0.39, 0.99)
Q5 (high)	4468	46	0.93 (0.55, 1.56)	2097	51	0.49 (0.29, 0.83)	2134	63	0.89 (0.55, 1.44)
P-trend[3]			0.80			0.027			0.41
Daidzein									
Q1 (low)	4698	47	1.00 (reference)	1881	56	1.00 (reference)	1849	58	1.00 (reference)
Q2	4767	37	0.77 (0.50, 1.21)	1864	50	0.86 (0.58, 1.29)	1856	44	0.73 (0.48, 1.10)
Q3	4795	47	0.99 (0.64, 1.54)	1839	43	0.67 (0.43, 1.05)	1847	47	0.80 (0.53, 1.22)
Q4	4719	48	0.97 (0.61, 1.54)	1921	49	0.69 (0.43, 1.10)	1912	37	0.58 (0.36, 0.92)
Q5 (high)	4607	40	0.77 (0.45, 1.33)	1954	51	0.58 (0.33, 1.01)	1995	63	0.92 (0.56, 1.52)
P-trend[3]			0.70			0.042			0.47
Genistein									
Q1 (low)	4698	48	1.00 (reference)	1866	56	1.00 (reference)	1846	60	1.00 (reference)
Q2	4775	34	0.69 (0.44, 1.09)	1869	50	0.86 (0.57, 1.28)	1853	41	0.65 (0.43, 0.99)
Q3	4795	48	0.99 (0.64, 1.54)	1822	42	0.68 (0.42, 1.03)	1846	45	0.74 (0.49, 1.14)
Q4	4717	50	0.99 (0.63, 1.57)	1938	48	0.67 (0.42, 1.07)	1915	39	0.59 (0.37, 0.94)
Q5 (high)	4601	39	0.73 (0.43, 1.27)	1964	53	0.61 (0.35, 1.05)	1999	64	0.91 (0.58, 1.50)
P-trend[3]			0.76			0.052			0.57

[1] Diagnosis of type 2 diabetes were based on self-report.

[2] Adjusted for age (y, continuous), study area (9 areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27 kg/m²), smoking habit (never, past, current with a consumption of <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men; and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), leisure time physical activity (<once/mo, 1–3 times/mo, or ≥once/wk), history of hypertension (yes or no), coffee consumption (almost never, <1 cup/d, 1 cup/d, or ≥2 cups/d), green tea consumption (almost never, <1 cup/d, 1 cup/d, 2–3 cups/d, or ≥4 cups/d), magnesium intake (mg/d, continuous), calcium intake (mg/d, continuous), vegetable intake (g/d, continuous), fiber intake (g/d, continuous), fish intake (g/d, continuous), and total energy intake (kJ/d, continuous).

[3] Based on multiple logistic regression analysis, assigning ordinal numbers 0–4 to the quintile categories of soy product, daidzein, or genistein intakes.

isoflavones may not play an important role in the pathogenesis of type 2 diabetes in men.

The mechanism by which isoflavones exert their antidiabetic effect is unclear. Isoflavones are structurally similar to endogenous estrogens and thus have a weak estrogenic effect by binding to the intranuclear estrogen receptors in various tissues (26,27). Estrogen has been suggested to participate in glucose homeostasis by modulating the expression of genes that are involved in insulin sensitivity and glucose uptake (32). Further, estrogen is a major regulator of adipocyte development and adipocyte number and inhibits lipogenesis by reducing the activity of lipoprotein lipase, an enzyme that regulates lipid uptake by adipocytes (27). Isoflavones may also affect glucose metabolism by nonestrogen receptor-mediated mechanisms (26). For example, isoflavones have been reported to have an antidiabetic effect through activation of PPAR, nuclear receptors that participate in cellular lipid homeostasis and insulin action (4). In addition to their estrogenic activity, isoflavones may inhibit intestinal glucose uptake, prevent glucose-induced lipid peroxidation, and improve basal metabolic rate and energy metabolism (26). Further, soy protein may improve insulin resistance and reduce adiposity by inhibiting insulin secretion from pancreatic β cells or by inhibiting lipogenesis and increasing lipolysis in the liver and adipocytes (26).

Strengths of the present study include our large sample size, the population-based prospective design, the use of a validated FFQ, and extensive adjustment of potentially important confounding factors, including obesity, smoking habit, family history of diabetes, and total energy. However, several limitations to the present study warrant mention. First, the diagnosis of type 2 diabetes was ascertained by self-report. However, a validation study conducted among our study population showed fairly good agreement between self-reported diabetes and diabetes documented in medical records (94%) and sensitivity of self-reported diabetes was reasonably high (83%). Second, dietary intakes of soy products and isoflavones were measured at only 1 time point (the second survey, which is the baseline of the present analysis) and thus may not reflect long-term intake levels. Repeated assessment of diet over a long period of time prior to the onset of a disease will provide a better estimate of exposure status. Third, because soy foods are the sole source of isoflavones, our study could not differentiate the effect of isoflavones from other substances in soy foods. To address this issue, measurements of isoflavone concentrations in blood or urine are required.

In conclusion, the present study found no evidence to support the hypothesis that higher intakes of soy product and isoflavones prevent type 2 diabetes in either men or all women. However, we did observe associations suggestive of a protective role of these food factors in overweight women or, to a lesser extent, postmenopausal women. Our findings warrant further investigation.

Acknowledgments

We thank Drs. Yumi Matsushita (International Medical Center of Japan) and Masayuki Kato (Japan Foundation for the Promotion of International Medical Research Cooperation) for their helpful discussions. We also thank the Japan Public Health Center-based Prospective Study Group for their contributions to the manuscript. S.T. was involved in the design of study as the principal investigator. M.I. and S.T. conducted the survey. A.N., T.M., Y.T., K.K., and M.N. drafted the plan for the data analyses. A.N. conducted data analysis. T.M. provided statistical expertise, and A.N. drafted the manuscript. A.N. had primary responsibility for final content. All authors were involved in interpretation of the results and revision of the manuscript and all approved the final version.

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