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Low-carbohydrate diet and risk of cancer incidence: The Japan Public Health Center-based prospective study

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Abstract

Epidemiological evidence on the effects of a long-term low-carbohydrate diet (LCD) on cancer incidence remains sparse. We investigate the association between LCD and the risk of overall and specific cancer site incidence in a Japanese population-based prospective cohort study among 90 171 participants aged 45-74. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). During a median 17.0 y of follow-up, we identified 15 203 cancer cases. A higher overall LCD score was associated with increased overall cancer risk (HR = 1.08 [CI: 1.02-1.14], *P*-trend = .012), while it was associated with decreased gastric cancer (GC) risk (0.81 [0.71-0.93], *P*-trend = .006). A higher animal-based LCD score was associated with higher risk of overall cancer (1.08 [1.02-1.14], *P*-trend = .003), colorectal cancer (CRC) (1.11 [0.98-1.25], *P*-trend = .018), rectal cancer (RC) (1.24 [1.00-1.54], *P*-trend = .025), lung cancer (LC) (1.16 [1.00-1.34], *P*-trend = .042), and lower risk of GC (0.90 [0.79-1.01], *P*-trend = .033). Furthermore, we found that plant-based LCD score was related to lower GC incidence (0.87 [0.77-0.99], *P*-trend = .031). Additionally, adjusted for plant fat intake amplified the adverse associations (overall cancer: 1.08 [1.02-1.14] vs. 1.11 [1.05-1.18]; CRC: 1.08 [0.95-1.22] vs. 1.13 [0.99-1.30]; LC: 1.14 [0.98-1.33] vs. 1.19 [1.01-1.41]). We conclude that LCD enriching with animal products was associated with increased overall cancer, CRC, and LC incidence. These adverse associations could be attenuated by plant fat consumption. LCD reduces the risk of developing GC. Long-term adherence to LCD without paying attention to the balance between animal and plant food source consumption might cause adverse overall cancer incidence consequences.

Abbreviations: BMI, body mass index; CIs, confidence intervals; CRC, colorectal cancer; ER−, estrogen receptor negative; FFQ, food frequency questionnaire; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*; HCAs, heterocyclic amines; HPFS, Health Professionals Follow-up Study; HRs, hazard ratios; IGF-1, insulin-like growth factor-1; JPHC, Japan Public Health Center-based Prospective Study; LC, lung cancer; LCD, low-carbohydrate diet; LCHP, low carbohydrate and high protein; NHS, Nurses' Health Study; NOCs, *N*-nitroso compounds; PAHs, polycyclic aromatic hydrocarbons; PHC, public health center; RC, rectal cancer.

KEYWORDS
Asian population, cancer incidence, low-carbohydrate diet, prospective cohort study, specific cancer site incidence

1 | INTRODUCTION

Although a balanced diet has been recommended for health through various studies,[1] diet low in carbohydrates and high in protein is still a popular option for weight loss and weight control. Such a LCD emphasizes the reduction of carbohydrate intake while encouraging increased intake of high-protein animal products that therefore contain high amounts of fat. When the intake of one macronutrient is high, the others will become low. Carbohydrates, protein, and fat are the 3 main macronutrients. Their effect on health should be evaluated as a whole rather than only focus on a single macronutrient. Therefore, a simple LCD summary score approach based on the percentage of energy from carbohydrate, protein, and fat were raised.[2] As is well known, cancer is a disease that develops with years of potentially dangerous exposure to factors, including dietary habits. Several previous studies have investigated the association between a LCD and cancer morbidity or mortality.[3-5] The NHS in the USA suggested that LCD with high plant protein and fat was associated with a decreased incidence of ER− breast cancer in postmenopausal women.[3] Moreover, cohort studies in the USA demonstrated that a higher overall LCD score and a higher animal-based LCD score are related to higher cancer mortality.[4] In contrast, the JPHC study showed no association between LCD and cancer mortality.[5] To date, the long-term safety of LCD remains controversial, and the evidence on how LCD affects cancer incidence remains sparse.

Therefore, in this large Japanese population-based cohort study, we used the LCD score to evaluate the association between LCD and the risk of overall and specific cancer site incidence.

2 | MATERIALS AND METHODS

2.1 | Study population

The JPHC study was initiated in 1990 for cohort I and in 1993 for cohort II, at 11 PHC areas.[6] In the baseline study, 140 420 participants were informed of the objectives of the study, and the completion of the survey questionnaire was regarded as providing consent to participate. A self-administered questionnaire was administered at the baseline, 5-y, and 10-y follow-ups. In this study, we took the 5-y follow-up survey as the starting point because it includes more comprehensive information on food intake.

Initially, the participants from the Tokyo area were not included because information on cancer incidence was unavailable (n = 7097). After excluding ineligible participants (non-Japanese nationality, late report of migration occurring before the start of the study, incorrect birth date, or lost to follow-up), 130 777 participants remained. Of these, 98 503 participants returned the 5-y questionnaire survey. We then excluded 1074 participants who did not respond to the food intake questions; 2514 participants who reported or were diagnosed with cancer before the 5 y follow-up questionnaire survey; and 4744 participants with energy intake at the upper or lower 2.5%. Finally, 90 171 participants were included in the present study.

2.2 | Food frequency questionnaire

The FFQ included 138 food items, and 9 beverage items, and was used to assess the average dietary food and beverage intake. Participants were asked about the frequency and portion size for each item consumed over the previous year.[7] The daily food consumption (g/d) was calculated by multiplying the consumption frequency by the typical portion size. Food and nutrient intake was estimated using the Standard Table of Food consumption in Japan (7th revised and enlarged edition).[8]

The validity of the FFQ was assessed using either 14-d or 28-d dietary records. Spearman correlation coefficients between energy-adjusted intake for carbohydrate, fat, and protein derived from the FFQ, and those derived from dietary records were 0.66-0.69, 0.55-0.57, and 0.30-0.31, respectively, in men and 0.45-0.47, 0.39-0.46, and 0.24-0.33, respectively, in women.[9] The reproducibility of estimations for intake of carbohydrate, fat, and protein between the 2 FFQs administered 1 y apart was 0.45-0.55, 0.47-0.57, and 0.47-0.57, respectively, in men, and 0.41-0.50, 0.38-0.52, and 0.32-0.54, respectively, in women.[10,11] Furthermore, we estimated protein and fat intakes from animal and plant sources separately. Animal food included fish and shellfish, meat and processed meat, egg, milk and dairy products, and butter, and plant food included foods other than animal food. When we assessed the validity and reproducibility of animal or plant protein and fat derived from FFQ, the Spearman correlation coefficients between % energy of animal protein, animal fat, plant protein, and plant fat derived from the FFQ, and those derived from the dietary records were 0.21, 0.42, 0.59, and 0.39, respectively, in men and 0.26, 0.42, 0.49, and 0.22, respectively, in women. The corresponding values between the 2 FFQs were 0.49, 0.53, 0.60, and 0.64, respectively, in men and 0.48, 0.53, 0.58, and 0.54, respectively, in women.[12]

2.3 | Assessment of LCD score

The method used to assess LCD score has been described elsewhere.[12] Briefly, according to the percentage of energy from carbohydrate, protein, or fat, participants were equally divided into 11 categories. For carbohydrate, participants from the lowest to highest category scored 10-0 points, while for protein and fat,

they scored 0-10 points. The LCD score was calculated as the total score of carbohydrate, protein, and fat, ranging from 0 to 30 points. A higher LCD score represented a lower carbohydrate intake with higher protein and fat intake. We then created separate scores for animal protein, animal fat, plant protein, and plant fat. Similarly, the animal-based LCD score was defined as the total score of carbohydrate, animal protein, and animal fat. The plant-based LCD score was the total score of carbohydrate, plant protein, and plant fat.

2.4 | Follow-up and case identification

We followed the study participants from the date of the 5-y follow-up questionnaire survey until the date of moving out of the study area, date of death, date of diagnosis with cancer, or the end of follow-up (December 31, 2012, for Osaka; December 31, 2013, for Kochi and Nagasaki areas; December 31, 2015, for the other areas), whichever occurred first.

The JPHC study incidence data were obtained from medical records and cancer registries with permission from the respective local governments of each study area. Death certificates were used as supplementary sources. According to the Japan cancer statistics in 2018, we selected the top 10 cancer sites (excluding malignant lymphoma) and 2 most common gender-related cancer sites (prostate and breast) for specific cancer sites analyses. Cancer identification by site was assigned according to the International Classification of Diseases for Oncology, 3rd edition[13] as follows: GC (C16), CRC (C18-C20), colon cancer (C18), RC (C19; C20), liver cancer (C22.0), pancreatic cancer (C25), LC (C34), esophageal cancer (C15), biliary tract cancer (C22.1; C23; C24), kidney cancer (C64), bladder cancer (C67), upper urinary tract cancer (C65; C66), prostate cancer (C61), and breast cancer (C50).

2.5 | Statistical analysis

Study participants were grouped into quintiles of overall LCD score, animal-based LCD score, and plant-based LCD score. Cox proportional hazards models were used to estimate HRs and 95% CIs to verify overall cancer and specific cancer site risk. The test for a linear trend was performed by entering the median value of each category into the model. All *P*-values were two-sided, and all statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc). We imputed missing data for covariates (BMI, smoking status, alcohol consumption, physical activity, coffee consumption, and green tea consumption, use of exogenous female hormones) (women only), and menopausal status (women only) by including all covariates, follow-up duration, and outcome in the model for multiple imputations (SAS PROC MI).[14] We performed 10 rounds of imputation, then combined the estimates and *P*-trend values according to the Rubin rule (SAS PROC MIANALYZE).[14,15]

We adjusted for age (continuous), sex, and area in Model 1. Model 2 was further adjusted for the following: smoking status (never, past, current with <20 cigarettes, 20-40 cigarettes, ≥40 cigarettes); alcohol consumption (none, occasional, regular of 1-150, 150-300, 300-450, >450 g alcohol/wk); BMI (<23, 23-25, 25-27, ≥27 kg/m^2), history of diabetes mellitus (yes or no), total physical activity levels (Met-h/d, quartiles), total energy intake (kcal/d, quintiles), green tea consumption (never, <1 cup/d, 1 cup/d, 2-3 cups/d, ≥4 cups/d), and coffee consumption (never, <1 cup/d, 1 cup/d, 2-3 cups/d, ≥4 cups/d). For breast cancer in women, Model 2 simplified the categories for smoking status (never, past, current) and alcohol consumption (none, occasional, regular of 1-150, >150 g alcohol/wk), and contained 2 other covariables: use of exogenous female hormones (yes or no) and menopausal status (premenopausal, natural menopause, surgical menopause). Based on Model 2, Model 3 was further adjusted for sodium intake (quintiles) for GC. We tested the interaction for each LCD score with sex before analyzing the association between LCD score and risk of overall cancer and specific cancer site. To examine the effect of protein and fat intakes on cancer risk, we further adjusted for animal protein, animal fat, plant protein, and plant fat (% energy, quintiles). The correlation coefficients among these 4 macronutrients were tested before the adjustment. In sensitivity analyses, the above analyses were repeated after excluding cancer cases that were diagnosed in the first 3 y. Additionally, 32 335 participants from cohort II provided blood specimens at the date of baseline survey. Of them, 17 507 participants in our current study had undergone a *H. pylori* infection test and had atrophic gastritis status. We described the GC case distribution for this subpopulation, and then conducted subgroup analyses for the relationship between LCD score and GC risk in *H. pylori* antibody-positive participants (N = 11 934) with further adjustment for *H. pylori* antibody concentration (tertiles) and atrophic gastritis status (none, moderate, and severe) based on Model 2.

3 | RESULTS

Of 90 171 participants, we ascertained 15 203 cancer cases during a median 17.0 y of follow-up (1 418 371 person years). Participants in the highest quintile of any kind of LCD score tended to have a history of diabetes, higher total energy intake and consumed more coffee and green tea. Participants with higher overall LCD score or animal-based LCD score consumed more animal protein, animal fat, and plant fat, but less plant protein. Participants with higher plant-based LCD score had higher protein and fat consumption, but the amounts and gradients were lower than those in the overall LCD score and animal-based LCD score (Table 1).

Table 2 shows the association between LCD score and the risk of overall cancer and site-specific cancer. Higher overall LCD score was associated with increased overall cancer risk (HR = 1.08 [CI: 1.02-1.14], *P*-trend = .012), while it was associated with decreased GC risk (0.81 [0.71-0.93], *P*-trend = .006). A null association was observed in other cancers. Furthermore, a higher animal-based LCD score was associated with higher risk of overall cancer (1.08 [1.02-1.14], *P*-trend = .003), CRC (1.11 [0.98-1.25], *P*-trend = .018),

TABLE 1 Characteristics of participants according to quintiles of LCD score

	Overall LCD score[a]			Animal-based LCD score[a]			Plant-based LCD score[a]		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
No. of subjects	17 410	17 685	17 495	19 030	16 663	19 125	18 531	16 304	18 000
Median score (range)	4 (2-5)	15 (14-16)	26 (24-28)	3 (1-5)	15 (14-16)	26 (25-28)	8 (6-9)	15 (14-16)	22 (21-24)
Age (y), mean ± SD	58.1 ± 8.2	57.0 ± 7.8	57.6 ± 7.8	58.1 ± 8.1	57.1 ± 7.8	57.3 ± 7.8	57.9 ± 8.2	57.1 ± 7.8	57.6 ± 7.7
Sex (men, %)	44.7	50.4	46.3	46.0	49.5	46.8	50.2	48.9	49.7
BMI (kg/m^2), mean ± SD	23.4 ± 3.1	23.5 ± 3.0	23.6 ± 3.0	23.4 ± 3.1	23.5 ± 3.0	23.6 ± 3.1	23.4 ± 3.1	23.4 ± 3	23.6 ± 3.0
Current smoker (%)	23.3	24.9	21.0	22.9	24.8	22.7	27.3	24.0	21.5
Alcohol consumption (≥1 time/wk, %)	32.4	41.4	35.6	30.5	41.5	39.0	40.8	39.0	36.5
Physical activity (MET-h/d)	32.4 ± 6.4	32.6 ± 6.3	32.2 ± 6.2	32.4 ± 6.3	32.5 ± 6.3	32.2 ± 6.2	32.2 ± 6.4	32.5 ± 6.3	32.4 ± 6.2
History of diabetes (yes, %)	3.6	4.9	5.9	3.9	5.1	5.5	4.1	4.6	6.4
Coffee consumption (≥1 cup/d, %)	27.4	34.9	34.0	27.1	35.0	35.0	30.0	33.4	34.1
Green tea consumption (≥1 cup/d, %)									
Sencya	51.0	59.0	60.0	54.3	58.6	56.6	46.0	58.9	64.6
Bancya	43.2	42.4	44.5	43.0	43.1	43.9	42.8	43.0	44.4
Dietary intake									
Total energy intake (kcal/d)	1705.8 ± 548.5	1997.7 ± 568.1	2292.3 ± 681.8	1745.3 ± 565.3	1989.3 ± 573.4	2280.3 ± 675.9	1809.5 ± 587.6	2030.0 ± 607.3	2135.5 ± 644.2
Carbohydrate (% energy/d)	66.0 ± 6.0	54.5 ± 5.9	44.1 ± 5.9	65.6 ± 5.7	54.3 ± 5.9	43.9 ± 6.2	59.8 ± 9.6	54.2 ± 9.0	50.2 ± 6.9
Protein (% energy/d)									
Animal protein	4.6 ± 1.5	7.5 ± 1.5	11.3 ± 2.6	4.5 ± 1.4	7.5 ± 1.3	11.3 ± 2.4	6.6 ± 2.7	7.9 ± 2.8	8.2 ± 2.6
Plant protein	7.2 ± 1.1	6.7 ± 1.3	6.1 ± 1.7	7.7 ± 1.3	6.7 ± 1.2	5.6 ± 1.2	6.0 ± 1.0	6.6 ± 1.3	7.8 ± 1.5
Fat (% energy/d)									
Animal fat	8.0 ± 3.0	13.6 ± 3.2	21.3 ± 5.7	7.6 ± 2.5	13.5 ± 2.5	22.1 ± 5.2	12.2 ± 5.6	14.6 ± 6.1	14.6 ± 5.2
Plant fat	8.9 ± 2.8	11.3 ± 3.2	13.0 ± 3.7	10.1 ± 3.6	11.3 ± 3.5	11.8 ± 3.3	7.3 ± 1.9	11.0 ± 1.8	15.3 ± 3.2
Red meat and processed meat (g/d)[b]	27.2 ± 19.5	46.9 ± 27.2	75.3 ± 47	25.3 ± 17.7	46.1 ± 25.1	79.2 ± 47.8	38.6 ± 28.3	52.5 ± 37.7	51.7 ± 35.9
Vegetables (g/d)[b]	192.7 ± 134.3	223.9 ± 134.7	230.6 ± 132.4	220.3 ± 159.7	221.8 ± 128.0	207.8 ± 116.0	145.7 ± 87.7	215.8 ± 110.9	296.7 ± 169.1

TABLE 1 (Continued)

	Overall LCD score[a]			Animal-based LCD score[a]			Plant-based LCD score[a]		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Fruits (g/d)[b]	256.9 ± 231.0	216.0 ± 153.5	176.1 ± 120.7	262.1 ± 224.4	214.4 ± 154.5	167.0 ± 119.2	216.4 ± 211.1	215.2 ± 158.9	211.2 ± 140.1
Sodium (g/d)[b]	11.0 ± 4.0	12.3 ± 3.7	13.4 ± 10.6	11.8 ± 4.3	12.1 ± 3.7	12.8 ± 14.9	9.7 ± 3.1	12.5 ± 12.3	14.3 ± 4.2
Use of exogenous female hormones (yes, %)[c]	2.4	2.5	2.6	2.4	2.7	2.6	2.5	2.4	3.1
Postmenopausal (yes, %)[c]	72.4	71.8	71.7	73.3	72.1	70.4	71.6	72.0	73.7

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); LCD, low-carbohydrate diet; MET, metabolic equivalents.

[a]Number of missing were 2234 for BMI, 5284 for smoking status, 2042 for alcohol consumption, 3016 for physical activity, 4802 for coffee consumption, 3568 for sencya and 3916 for bancya consumption, 2752 women were missing for use of exogenous female hormones, and 2963 for menopausal status.

[b]Adjusted for total energy intake using residual method.

[c]Women only.

RC (1.24 [1.00-1.54], *P*-trend = .025), and LC (1.16 [1.00-1.34], *P*-trend = .042), and lower risk of GC (0.90 [0.79-1.01], *P*-trend = .033). Another, we found that plant-based LCD score were related to lower GC incidence (0.87 [0.77-0.99], *P*-trend = .031). No interactions for LCD score with sex were observed (*P*-interaction > .1). The results remained unchanged after further adjustment for sodium intake for GC or after excluding 1654 cancer cases diagnosed in the first 3 y in sensitivity analyses.

Table 3 shows the association between the overall LCD score and the risk of overall cancer, GC, CRC, and LC after additional adjustment for animal protein, animal fat, plant protein, or plant fat based on Model 2. Pearson correlation coefficients among these 4 macronutrients were 0.75 for animal protein and animal fat, and <0.5 for any other 2. Adjustment for animal protein intake attenuated the adverse associations (overall cancer: 1.08 [1.02-1.14], *P*-trend = .012 vs. 1.03 [0.95-1.13], *P*-trend = .604; CRC: 1.08 [0.95-1.22], *P*-trend = .176 vs. 1.02 [0.83-1.25], *P*-trend = .798; LC: 1.14 [0.98-1.33], *P*-trend = .170 vs. 1.00 [0.78-1.29], *P*-trend = .850). In contrast, adjusted for plant fat intake amplified the adverse associations (overall cancer: 1.08 [1.02-1.14], *P*-trend = .012 vs. 1.11 [1.05-1.18], *P*-trend = .001; CRC: 1.08 [0.95-1.22], *P*-trend = .176 vs. 1.13 [0.99-1.30], *P*-trend = .040; LC: 1.14 [0.98-1.33], *P*-trend = .170 vs. 1.19 [1.01-1.41], *P*-trend = .055).

Among the subgroup, among the 17 507 participants who had *H. pylori* infection test and atrophic gastritis status, approximately two-thirds (n = 11 934) were *H. pylori* antibody-positive. In total, 391 cases (92.2%) were *H. pylori* antibody-positive among the 424 cases of GC. Although the number of cases was limited, a substantially decreased GC risk was linked to a higher overall LCD score and animal-based LCD score (0.67 [0.47-0.95], *P*-trend = .029; 0.68 [0.49-0.96], *P*-trend = .021, respectively) in the *H. pylori* antibody-positive subpopulation (Table S1).

4 | DISCUSSION

In this population-based cohort study, the overall LCD score was associated with increased overall cancer risk and reduced GC risk. When considering the LCD score based on animal or plant sources of protein and fat, we found the animal-based LCD score was correlated with increased overall cancer risk, marginally significant increase in CRC, RC, and LC risk, and a marginally significant decrease in GC risk. Furthermore, a higher plant-based LCD score was associated with a decreased incidence of GC.

To the best of our knowledge, only a few studies have investigated the association between LCD and cancer incidence. Our study is the first prospective study to evaluate the association between LCD and subsequent cancer incidence in Asia. To date, there have been only 3 prospective studies that have assessed the association between LCD and cancer incidence.[3,16,17] The Nurse Health Study observed that a diet moderate in carbohydrate and high in plant protein and fat was related to a decreased ER− breast cancer incidence.[3] However, the other 2 studies from Sweden only considered LCHP

TABLE 2 Hazard ratio (95% confident interval) of incidence of overall cancer and site-specific cancer according to quintiles of LCD score

	Overall LCD score				Animal-based LCD score				Plant-based LCD score			
Cancer type	Q1	Q3	Q5	*P*-trend[a]	Q1	Q3	Q5	*P*-trend[a]	Q1	Q3	Q5	*P*-trend[a]
No of subjects	17 410	17 685	17 495		19 030	16 663	19 125		18 531	16 304	18 000	
Median score (range)	4 (2-5)	15 (14-16)	26 (24-28)		3 (1-5)	15 (14-16)	26 (25-28)		8 (6-9)	15 (14-16)	22 (21-24)	
Person years	271 389	277 554	276 294		276 205	261 155.02	301 490.86		281 982	258 195.43	285 758.38	
Overall cancer, cases	2891	2997	3051		3195	2826	3322		3177	2766	3100	
Model 1	1.00	1.04 (0.98-1.09)	1.07 (1.01-1.12)	.080	1.00	1.05 (1.00-1.11)	1.09 (1.04-1.14)	.001	1.00	0.98 (0.93-1.03)	0.96 (0.91-1.01)	.045
Model 2	1.00	1.02 (0.97-1.08)	1.08 (1.02-1.14)	.012	1.00	1.03 (0.98-1.08)	1.08 (1.02-1.14)	.003	1.00	0.99 (0.94-1.05)	0.99 (0.94-1.05)	.734
3 y exclusion, cases	2540	2709	2701		2815	2538	2946		2816	2471	2755	
Model 2	1.00	1.05 (0.99-1.11)	1.09 (1.03-1.15)	.009	1.00	1.04 (0.99-1.10)	1.09 (1.03-1.15)	.002	1.00	0.99 (0.94-1.05)	0.99 (0.93-1.05)	.544
Gastric cancer, cases	569	500	448		621	457	516		554	434	476	
Model 1	1.00	0.88 (0.78-0.99)	0.83 (0.73-0.94)	.006	1.00	0.89 (0.79-1.00)	0.93 (0.83-1.05)	.095	1.00	0.88 (0.77-1.00)	0.86 (0.76-0.97)	.007
Model 2	1.00	0.86 (0.76-0.97)	0.81 (0.71-0.93)	.006	1.00	0.86 (0.76-0.97)	0.90 (0.79-1.01)	.033	1.00	0.88 (0.77-1.00)	0.87 (0.77-0.99)	.031
Model 3	1.00	0.84 (0.74-0.95)	0.79 (0.69-0.91)	.002	1.00	0.85 (0.75-0.96)	0.89 (0.78-1.00)	.023	1.00	0.85 (0.74-0.97)	0.82 (0.71-0.95)	.004
Colorectal cancer, cases	550	549	551		604	518	627		583	545	574	
Model 1	1.00	1.00 (0.89-1.13)	1.02 (0.91-1.15)	.773	1.00	1.03 (0.92-1.16)	1.10 (0.99-1.24)	.022	1.00	1.03 (0.92-1.16)	0.95 (0.85-1.07)	.042
Model 2	1.00	1.00 (0.88-1.13)	1.08 (0.95-1.22)	.176	1.00	0.99 (0.88-1.12)	1.11 (0.98-1.25)	.018	1.00	1.08 (0.96-1.21)	1.03 (0.91-1.17)	.701
Colon cancer, cases	393	380	385		435	358	428		411	392	384	
Model 1	1.00	0.98 (0.85-1.13)	1.01 (0.87-1.16)	.610	1.00	1.00 (0.87-1.15)	1.06 (0.92-1.21)	.185	1.00	1.04 (0.91-1.20)	0.89 (0.77-1.03)	.015
Model 2	1.00	0.97 (0.84-1.12)	1.04 (0.90-1.21)	.815	1.00	0.96 (0.83-1.11)	1.06 (0.92-1.22)	.170	1.00	1.08 (0.94-1.24)	0.95 (0.82-1.10)	.184
Rectal cancer, cases	157	169	166		169	160	199		172	153	190	
Model 1	1.00	1.06 (0.85-1.32)	1.07 (0.86-1.33)	.188	1.00	1.11 (0.90-1.38)	1.23 (1.00-1.51)	.030	1.00	1.00 (0.80-1.25)	1.10 (0.89-1.35)	.992

TABLE 2 (Continued)

Cancer type	Overall LCD score				Animal-based LCD score				Plant-based LCD score			
	Q1	Q3	Q5	*P*-trend[a]	Q1	Q3	Q5	*P*-trend[a]	Q1	Q3	Q5	*P*-trend[a]
Model 2	1.00	1.07 (0.85-1.33)	1.15 (0.91-1.46)	.034	1.00	1.08 (0.86-1.34)	1.24 (1.00-1.54)	.025	1.00	1.08 (0.86-1.34)	1.25 (1.00-1.56)	.185
Liver cancer, cases	103	140	119		108	142	133		159	132	128	
Model 1	1.00	1.41 (1.09-1.82)	1.25 (0.95-1.63)	.271	1.00	1.61 (1.25-2.07)	1.36 (1.05-1.76)	.097	1.00	1.02 (0.81-1.29)	0.90 (0.71-1.14)	.381
Model 2	1.00	1.45 (1.11-1.88)	1.24 (0.94-1.64)	.264	1.00	1.64 (1.27-2.12)	1.34 (1.03-1.75)	.134	1.00	1.06 (0.83-1.34)	0.93 (0.72-1.19)	.652
Pancreatic cancer, cases	116	111	109		125	110	115		105	93	127	
Model 1	1.00	0.97 (0.75-1.27)	0.94 (0.73-1.23)	.571	1.00	1.06 (0.82-1.37)	0.96 (0.74-1.24)	.544	1.00	1.02 (0.77-1.34)	1.21 (0.93-1.58)	.327
Model 2	1.00	0.96 (0.73-1.25)	0.93 (0.70-1.23)	.544	1.00	1.03 (0.79-1.34)	0.92 (0.70-1.21)	.389	1.00	1.05 (0.79-1.39)	1.28 (0.98-1.69)	.161
Lung cancer, cases	368	390	404		400	373	434		415	351	373	
Model 1	1.00	1.05 (0.91-1.22)	1.09 (0.94-1.26)	.466	1.00	1.11 (0.97-1.28)	1.13 (0.98-1.29)	.083	1.00	0.97 (0.84-1.11)	0.88 (0.76-1.01)	.081
Model 2	1.00	1.05 (0.91-1.22)	1.14 (0.98-1.33)	.170	1.00	1.11 (0.96-1.28)	1.16 (1.00-1.34)	.042	1.00	0.99 (0.85-1.14)	0.92 (0.80-1.07)	.379
Esophageal cancer, cases	76	79	82		77	82	95		110	88	86	
Model 1	1.00	0.96 (0.70-1.32)	1.07 (0.78-1.46)	.195	1.00	1.21 (0.89-1.66)	1.29 (0.95-1.75)	.983	1.00	0.86 (0.65-1.15)	0.74 (0.56-0.99)	.008
Model 2	1.00	1.00 (0.73-1.39)	1.39 (1.00-1.94)	.352	1.00	1.13 (0.82-1.55)	1.39 (1.01-1.90)	.492	1.00	1.03 (0.78-1.38)	1.07 (0.79-1.44)	.883
Biliary tract cancer, cases	113	104	113		136	95	119		120	120	108	
Model 1	1.00	0.97 (0.74-1.26)	1.03 (0.79-1.34)	.948	1.00	0.88 (0.68-1.15)	0.96 (0.75-1.23)	.984	1.00	1.11 (0.86-1.43)	0.84 (0.65-1.10)	.415
Model 2	1.00	0.93 (0.71-1.23)	0.97 (0.73-1.28)	.725	1.00	0.84 (0.64-1.10)	0.89 (0.68-1.16)	.580	1.00	1.10 (0.85-1.42)	0.82 (0.62-1.08)	.343
Kidney cancer, cases	36	49	50		44	39	48		44	38	48	
Model 1	1.00	1.26 (0.82-1.94)	1.27 (0.83-1.96)	.710	1.00	1.00 (0.65-1.54)	1.05 (0.69-1.59)	.843	1.00	0.90 (0.58-1.39)	0.95 (0.63-1.44)	.975

(Continues)

TABLE 2 (Continued)

Cancer type	Overall LCD score				Animal-based LCD score				Plant-based LCD score			
	Q1	Q3	Q5	*P*-trend[a]	Q1	Q3	Q5	*P*-trend[a]	Q1	Q3	Q5	*P*-trend[a]
Model 2	1.00	1.24 (0.80-1.92)	1.23 (0.78-1.94)	.879	1.00	1.01 (0.65-1.56)	1.07 (0.69-1.64)	.889	1.00	0.85 (0.55-1.32)	0.85 (0.55-1.31)	.591
Bladder cancer, cases	78	88	81		85	79	84		100	60	88	
Model 1	1.00	1.07 (0.79-1.45)	1.01 (0.74-1.39)	.842	1.00	1.09 (0.80-1.48)	1.04 (0.77-1.41)	.888	1.00	0.65 (0.47-0.90)	0.80 (0.60-1.08)	.162
Model 2	1.00	1.03 (0.76-1.41)	1.00 (0.72-1.39)	.806	1.00	1.06 (0.77-1.44)	1.03 (0.75-1.41)	.807	1.00	0.64 (0.46-0.89)	0.78 (0.58-1.07)	.149
Upper urinary tract cancer, cases	19	21	18		20	27	20		22	22	18	
Model 1	1.00	1.06 (0.57-1.98)	0.89 (0.47-1.72)	.608	1.00	1.54 (0.86-2.76)	0.98 (0.52-1.83)	.701	1.00	1.08 (0.60-1.96)	0.77 (0.41-1.44)	.218
Model 2	1.00	0.99 (0.52-1.86)	0.88 (0.44-1.73)	.588	1.00	1.46 (0.81-2.63)	0.97 (0.51-1.86)	.690	1.00	1.03 (0.56-1.89)	0.72 (0.37-1.39)	.178
Prostate cancer, cases[b]	232	298	300		261	256	300		280	270	315	
Model 1	1.00	1.14 (0.96-1.36)	1.18 (0.99-1.40)	.099	1.00	1.08 (0.91-1.29)	1.12 (0.95-1.32)	.076	1.00	1.05 (0.89-1.25)	1.04 (0.88-1.23)	.518
Model 2	1.00	1.12 (0.94-1.34)	1.17 (0.97-1.40)	.164	1.00	1.07 (0.90-1.28)	1.11 (0.93-1.32)	.111	1.00	1.04 (0.87-1.23)	1.02 (0.86-1.21)	.763
Breast cancer, cases[b]	157	169	188		181	161	198		158	183	177	
Model 1	1.00	1.09 (0.88-1.36)	1.14 (0.92-1.41)	.218	1.00	1.03 (0.83-1.28)	1.04 (0.85-1.27)	.384	1.00	1.15 (0.93-1.43)	1.01 (0.82-1.26)	.922
Model 2	1.00	1.09 (0.87-1.36)	1.10 (0.88-1.38)	.353	1.00	1.02 (0.82-1.26)	0.99 (0.80-1.23)	.658	1.00	1.14 (0.92-1.42)	0.99 (0.79-1.25)	.980

Abbreviations: LCD, low-carbohydrate diet.

Model 1 adjusted for age sex area.

Model 2 was further adjusted for smoking, drinking, BMI, total physical activity levels (MET-h/d), history of diabetes, total energy intake, green tea consumption, and coffee consumption.

[a]Linear trend across quintiles of LCD score was tested by entering the median values of each quintile into the Cox proportional hazards model.

[b]Prostate cancer was conducted in men; breast cancer was conducted in women, and were further adjusted for menopausal status (yes, no, natural; no, artificial), use of exogenous hormone pills (yes or no).

[c]Model 3 was further adjusted for sodium intake (quintile) for GC cancer based on Model 2.

TABLE 3 Hazard ratio (95% confident interval) of overall cancer, GC, CRC, and LC when further adjustment for macronutrient according to quintiles of overall LCD score

	Overall LCD score					
Cancer type	**Q1 (2-5)**	**Q2 (9-11)**	**Q3 (14-16)**	**Q4 (19-22)**	**Q5 (24-28)**	***P*-trend[a]**
Overall cancer						
Model 2	1.00	1.03 (0.97-1.08)	1.02 (0.97-1.08)	1.03 (0.97-1.08)	1.08 (1.02-1.14)	.012
Adjusted for animal protein	1.00	1.02 (0.97-1.08)	1.01 (0.94-1.08)	1.00 (0.92-1.08)	1.03 (0.95-1.13)	.604
Adjusted for animal fat	1.00	1.04 (0.98-1.10)	1.03 (0.97-1.10)	1.03 (0.96-1.10)	1.07 (0.99-1.16)	.162
Adjusted for plant protein	1.00	1.02 (0.97-1.08)	1.02 (0.97-1.08)	1.02 (0.97-1.08)	1.07 (1.01-1.13)	.058
Adjusted for plant fat	1.00	1.04 (0.98-1.09)	1.04 (0.99-1.10)	1.05 (0.99-1.11)	1.11 (1.05-1.18)	.001
GC						
Model 2	1.00	0.84 (0.75-0.95)	0.86 (0.76-0.97)	0.84 (0.74-0.95)	0.81 (0.71-0.93)	.006
Adjusted for animal protein	1.00	0.82 (0.71-0.94)	0.80 (0.68-0.95)	0.78 (0.65-0.95)	0.76 (0.61-0.95)	.034
Adjusted for animal fat	1.00	0.86 (0.76-0.99)	0.89 (0.76-1.03)	0.86 (0.72-1.02)	0.80 (0.65-0.97)	.058
Adjusted for plant protein	1.00	0.84 (0.74-0.95)	0.85 (0.75-0.97)	0.84 (0.74-0.95)	0.81 (0.70-0.93)	.007
Adjusted for plant fat	1.00	0.85 (0.76-0.97)	0.88 (0.77-1.00)	0.87 (0.76-1.00)	0.85 (0.73-0.98)	.065
CRC						
Model 2	1.00	1.00 (0.89-1.13)	1.00 (0.88-1.13)	1.06 (0.94-1.20)	1.08 (0.95-1.22)	.176
Adjusted for animal protein	1.00	1.00 (0.88-1.14)	0.99 (0.84-1.16)	1.03 (0.87-1.23)	1.02 (0.83-1.25)	.798
Adjusted for animal fat	1.00	1.02 (0.90-1.16)	1.00 (0.86-1.16)	1.04 (0.88-1.22)	1.04 (0.86-1.25)	.716
Adjusted for plant protein	1.00	0.99 (0.88-1.12)	0.98 (0.87-1.11)	1.04 (0.92-1.17)	1.04 (0.91-1.18)	.471
Adjusted for plant fat	1.00	1.02 (0.91-1.15)	1.03 (0.91-1.17)	1.11 (0.97-1.26)	1.13 (0.99-1.30)	.040
LC						
Model 2	1.00	0.99 (0.86-1.15)	1.05 (0.91-1.22)	0.97 (0.83-1.12)	1.14 (0.98-1.33)	.170
Adjusted for animal protein	1.00	0.96 (0.81-1.13)	0.97 (0.80-1.18)	0.87 (0.70-1.08)	1.00 (0.78-1.29)	.850
Adjusted for animal fat	1.00	0.94 (0.80-1.10)	0.93 (0.78-1.12)	0.82 (0.67-1.00)	0.93 (0.74-1.17)	.386
Adjusted for plant protein	1.00	0.98 (0.85-1.14)	1.03 (0.89-1.20)	0.94 (0.80-1.10)	1.08 (0.92-1.27)	.517
Adjusted for plant fat	1.00	1.01 (0.87-1.17)	1.07 (0.92-1.25)	1.00 (0.85-1.17)	1.19 (1.01-1.41)	.055

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; LC, lung cancer; LCD, low-carbohydrate diet.

[a]Linear trend across quintiles of LCD score was tested by entering the median values of each quintile into the Cox proportional hazards model.

intakes. One reported null associations with overall cancer and site-specific cancer incidence[16]; the other suggested that an LCHP diet was linked to lower prostate cancer incidence.[17] For mortality, a positive association has been found for animal-based LCD score and cancer mortality for pooling NHS and HPFS.[4] In cohort studies of Swedish women or Japanese adults,[5,18] neither showed a tendency toward a linear association between LCD score and cancer mortality. Taken together, the previous studies to date were not consistent in terms of the long-term effects of LCD on cancer risk.

In our study, a higher animal-based LCD score was related to higher overall cancer, CRC, RC, and LC risk. However, these associations disappeared for the plant-rich LCD score. Consistent with our findings, previous studies have noted that a higher incidence of CRC is related to a westernized dietary pattern, which favors a higher intake of animal products.[19,20] According to the World Cancer Research Fund's Cancer Report,[21] there is convincing evidence that high red meat and processed meat consumption are associated with increased CRC risk. A previous study in JPHC found an adverse association between red meat consumption and LC risk.[22] The biomedical plausibility is considerable. Red meat and processed meat would produce and contain carcinogens such as HCAs, PAHs, and NOCs during cooking or processing. These substances might act as pro-oxidants and, therefore, lead to carcinogenesis.[23-26] Vegetables, fruits, cereals, and legumes are the major sources of vitamins, dietary fibers, and carbohydrates. Vitamins have been proven to have anti-oxidant and anti-inflammatory properties.[27] Similarly, dietary fiber has anti-inflammatory properties[28]; some types could attenuate postprandial rises in blood glucose and insulin by reducing the rate of glucose absorption.[29] Therefore, an animal-based LCD might restrict healthy food consumption in the long run, causing the adverse effects of red meat to some extent. In the colon and rectal cancer analysis, we found that the animal-based LCD was strongly associated with increased RC risk. This finding was in line with previous studies on the association of red meat intake with CRC risk, which have also shown that NOCs from red meat or processed meat are more carcinogenic to the rectum than the colon.[30] Differences in rates of metabolism, fermentation, transit time, and expression of enzymes

and different morphology, are considered to be the reasons for the difference in the effect of a risk factor on the colon and rectum.[31] Alternatively, it has been pointed out that an LCD with higher animal product consumption would increase the levels of cancer-promoting metabolites.[32] A long-term higher intake of animal protein and fat is associated with increased insulin or IGF-1 levels, which are important tumor promoters, resulting in accelerated tumor cell proliferation.[33,34] This hypothesis also supports our findings that adjustment for animal protein attenuated the adverse association between overall LCD and cancer risk. Conversely, although the plant-based LCD score was not associated with overall cancer, CRC, or LC risk, the positive associations of overall LCD were aggravated when adjusting for plant fat intake. In addition, the adverse associations of overall LCD for overall cancer and CRC risk were only observed in the low plant fat intake groups when stratifying plant fat intake (Table S2). Therefore, we supposed that increased plant fat intake could offset the adverse effects of consuming animal foods. A previous study has reported that plant fat enriched with unsaturated fatty acids could improve insulin sensitivity and, in turn, reduce circulating insulin and markers of inflammation.[35]

The stomach is the main organ that digests proteins, therefore it has high acidity of gastric juice. Previous studies have noted that gastric juice ascorbic acid has a role in preventing the formation of NOCs, and, therefore, protects against GC.[36] It has been noted that the effects of carbohydrate and protein on stimulating gastric juice secretion are different; a low carbohydrate with moderate protein diet would prolong the gastric secretion duration, therefore, increasing the amount of gastric acid[37,38]; fresh fruits and vegetables are sources of ascorbic acid, which are linked to a reduction in stomach carcinogenesis.[39] Our study showed that LCD score was associated with reduced GC incidence. This finding is consistent with the JPHC study on dietary patterns, which suggested that the traditional Japanese dietary pattern with high rice consumption increased GC incidence.[40] Previous studies in JPHC have suggested that a higher salt content in food is positively associated with GC risk,[41] especially when typically consuming rice with salted foods.[40] However, in our study, the group with low-carbohydrate intake (Q5) had a higher sodium intake, and further adjustment for sodium intake did not change the results of the association between LCD score and GC (Model 3). Our findings may support the mechanism that carbohydrate restriction with high-protein intake could promote gastric acid secretion to prevent gastric carcinogenesis.[37] As there was a lack of data on *H. pylori* infection status for each subject, residual confounding of *H. pylori* might exist for the association between LCD score and GC.

H. pylori is an independent factor responsible for GC, and 65%–80% of all GC cases were caused by *H. pylori* infection.[42] In our subpopulation, 92.2% of GC cases were *H. pylori* positive. Therefore, we could not assess the *P*-value for interaction between LCD score and *H. pylori* infection because GC cases without *H. pylori* infections were limited. Analysis for the *H. pylori* antibody-negative population also failed to be conduct, which meant that the direct effect of LCD on the risk of GC is unknown. Compared with the associations in the whole population, the protective effects of overall and animal-based LCD on GC were more pronounced in the *H. pylori* antibody-positive population (Table S1). We speculated that interactions between foods and *H. pylori* might exist. Previous studies have revealed that a diet pattern high in sweets and carbohydrates was positively associated with prevalence of *H. pylori* infection.[43] The prevalence of *H. pylori*-related gastric precancerous lesions progressively increased with increased starchy vegetable intake and reduced fresh fruit intake.[44] It is supposed that a higher starchy food intake leads to an elevation in blood glucose level to reduce gastric acid secretion and subsequently creates an environment favorable for the growth and proliferation of *H. pylori* and other microorganisms.[45,46] Protein-enriched foods are potent stimulants of gastric acid secretion.[38] Therefore, for the *H. pylori* antibody-positive population, animal-based LCD had a more notable protective effect on GC through regulating the gastric acid secretion process to inhibit the growth and proliferation of *H. pylori*. However, a similar protective association for plant-based LCD in the whole population was not observed in the *H. pylori* antibody-positive population. Considering that the *H pylori* infection status could not be adjusted in the whole population analysis, residual confounding of *H. pylori* might exist, therefore the inverse association between plant-based LCD and GC should be interpreted with caution. Further investigations between LCD and GC risk in non-*H. pylori* infection populations are also warranted.

Our study had several strengths. This is a large, population-based, prospective study with a long follow-up period. The prospective design reduced recall bias and reverse causation. The reliable FFQ and available data from the questionnaire enabled us to calculate LCD scores and carefully adjust for important potential factors. Some limitations of our study warrant mention. First, due to the low validity of carbohydrate, protein, and fat intake, dietary information was assessed at a single time point, this caveat might have led to misclassification of LCD score. However, such misclassification tends to attenuate the association described in our study. Second, some participants in a subhealthy status might have changed their dietary behavior when answering the questionnaire. This may have obscured the relationship between LCD score and cancer risk. However, there was no material change in the results when we excluded the first 3 y of cancer cases in the sensitivity assessment. Third, as we could not adjust for some unmeasured covariables such as socioeconomic status and *H. pylori* infection status for the whole population, potential residual confounding might not have been ruled out completely.

In conclusion, LCD enriched with animal products was associated with increased overall cancer, CRC, and LC incidence, and these adverse associations could be attenuated by plant fat consumption. LCD reduces the risk of developing GC. Long-term adherence to a LCD without paying attention to the balance between animal and plant food source might cause adverse overall cancer incidence consequences. Because the evidence on the association between

LCD score and risk of cancer incidence is limited, further studies are warranted.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Cai: responsible for the data collection, statistical analysis, data interpretation, and manuscript drafting; Sobue, Kitamura, Ishihara, Nanri, Mizoue, Iwasaki, Yamaji, Inoue, Tsugane, Sawada: reviewed and edited the manuscript, data collection, and contributed to the discussion; Sawada: (principal investigator): obtained funding and designed, initiated, and organized the study, management of the study. All authors had primary responsibility for final content. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The Institutional Review Board of the National Cancer Center, Tokyo, Japan approved the JPHC study. The present study was approved by the Ethical Review Board of Osaka University, Osaka, Japan.

DATA AVAILABILITY STATEMENT

For information on how to apply to gain access to JPHC data, following the instructions at https://epi.ncc.go.jp/en/jphc/805/8155.html.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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