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

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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; HCA, 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.

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.
1 | INTRODUCTION

Although a balanced diet has been recommended for health through various studies, 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 three 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. 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. 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. 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. In contrast, the JPHC study showed no association between LCD and cancer mortality. 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. 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. 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). 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. The reproducibility of estimates for intake of carbohydrate, fat, and protein between the two 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. 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 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 two 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.

2.3 | Assessment of LCD score

The method used to assess LCD score has been described elsewhere. 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 site analyses. Cancer identification by site was assigned according to the International Classification of Diseases for Oncology, 3rd edition 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). We performed 10 rounds of imputation, then combined the estimates and P-trend values according to the Rubin rule (SAS PROC MIANALYZE).

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/m²), 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 = .014), 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),...
|                          | Overall LCD score<sup>a</sup> | Animal-based LCD score<sup>a</sup> | Plant-based LCD score<sup>a</sup> |
|--------------------------|-------------------------------|-----------------------------------|----------------------------------|
|                          | 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       | 570 ± 78         | 576 ± 78         | 58.1 ± 8.1       | 571 ± 7.8        | 573 ± 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<sup>2</sup>), 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 ± 3.0       | 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             |
| 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)<sup>b</sup> | 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)<sup>b</sup> | 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    |

<sup>a</sup> CAI et al.

<sup>b</sup> Median ± interquartile range.
Table 1 (Continued)

| Overall LCD score | Plant-based LCD score | Animal-based LCD score |
|-------------------|-----------------------|------------------------|
| Q1  | Q3   | Q5  | Q1  | Q3   | Q5  | Q1  | Q3   | Q5  |
| 748 | 702  | 702 | 748 | 702  | 702 | 748 | 702  | 702 |
| Fruits (g/d)      | 231.0 ± 153.5         | 216.0 ± 119.2          | 198.6 ± 102.7          |
| Sodium (g/d)      | 11.0 ± 5.4            | 12.3 ± 4.2             | 19.6 ± 7.2             |
| Use of exogenous female hormones (yes, %) | 72.4                  | 73.3                  | 71.6                  |
| Postmenopausal (yes, %) | 71.7                  | 71.8                  | 71.7                  |

Note: Adjusted for total energy intake using residual method.

**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. 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. However, the other 2 studies from Sweden only considered LCHP...
| Cancer type       | Overall LCD score | Animal-based LCD score | Plant-based LCD score |
|------------------|------------------|------------------------|-----------------------|
|                  | Q1   | Q3   | Q5   | Q1   | Q3   | Q5   | Q1   | Q3   | Q5   | Q1   | Q3   | Q5   |
| No of subjects   | 17410| 17685| 17495| 19030| 16663| 19125| 18531| 16304| 19125| 18000|
| Median score     | 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     | 271389| 277554| 276294| 276205| 261155.02| 301490.86| 281982| 258195.43| 285758.38|
| Overall cancer, cases | 2891 | 2997 | 3051 | 3195 | 2826 | 3322 | 3177 | 2766 | 3100 | 1.00 | 1.04 | (0.98-1.09) |
| Model 1          | 1.00 | 1.04 | 1.07 | 1.05 (1.10-1.11) | 1.09 (1.04-1.14) | .001 | 1.00 | 0.98 (0.93-1.10) | 0.96 (0.91-1.01) |
| Model 2          | 1.00 | 1.02 | 1.08 | 1.03 (0.98-1.08) | 1.08 (1.02-1.14) | .003 | 1.00 | 0.99 (0.94-1.10) | 0.99 (0.94-1.05) |
| Model 3          | 1.00 | 1.05 | 1.09 | 1.04 (0.99-1.10) | 1.09 (1.03-1.15) | .002 | 1.00 | 0.99 (0.94-1.10) | 0.99 (0.93-1.05) |
| 3 y exclusion, cases | 2540| 2709 | 2701 | 2815 | 2538 | 2946 | 2816 | 2471 | 2755 | 1.00 | 0.86 (0.76-0.97) | 0.82 (0.71-0.95) |
| Model 2          | 1.00 | 1.05 | 1.09 | 1.04 (0.99-1.10) | 1.09 (1.03-1.15) | .002 | 1.00 | 0.99 (0.94-1.10) | 0.99 (0.93-1.05) |
| Gastric cancer, cases | 569  | 500  | 448  | 621  | 457  | 516  | 554  | 434  | 476  | 1.00 | 0.88 (0.78-0.99) | 0.86 (0.76-0.97) |
| Model 1          | 1.00 | 0.88 | 0.83 | 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) |
| Model 2          | 1.00 | 0.86 | 0.81 | 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) |
| Model 3          | 1.00 | 0.84 | 0.79 | 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) |
| Colectal cancer, cases | 550  | 549  | 551  | 604  | 518  | 627  | 583  | 545  | 574  | 1.00 | 0.98 (0.85-1.13) | 0.95 (0.85-1.07) |
| Model 1          | 1.00 | 1.00 | 1.02 | 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) |
| Model 2          | 1.00 | 1.00 | 1.08 | 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) |
| Colon cancer, cases | 393  | 380  | 385  | 435  | 358  | 428  | 411  | 392  | 384  | 1.00 | 0.98 (0.85-1.13) | 0.89 (0.77-1.03) |
| Model 1          | 1.00 | 0.98 | 1.01 | 1.00 (0.87-1.15) | 1.06 (0.92-1.21) | .185 | 1.00 | 1.04 (0.91-1.10) | 0.89 (0.77-1.03) |
| Model 2          | 1.00 | 0.97 | 1.04 | 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) |
| Rectal cancer, cases | 157  | 169  | 166  | 169  | 160  | 199  | 172  | 153  | 190  | 1.00 | 1.06 (0.85-1.32) | 1.11 (0.89-1.13) |
| Model 1          | 1.00 | 1.06 | 1.07 | 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) |
### TABLE 2 (Continued)

| Cancer type                  | Overall LCD score | Animal-based LCD score | Plant-based LCD score |
|------------------------------|-------------------|------------------------|-----------------------|
|                              | Q1    | Q3    | Q5    | P-trenda | Q1    | Q3    | Q5    | P-trenda | Q1    | Q3    | Q5    | P-trenda |
| Liver cancer, cases          |       |       |       |          |       |       |       |          |       |       |       |          |
| Model 1                      | 1.00  | 1.07  | 1.15  | .034     | 1.00  | 1.08 (0.86-1.34) | 1.24 (1.00-1.54) | .025     | 1.19  | 1.32  | 1.28  | .381      |
| Model 2                      | 1.00  | 1.15  | 1.25  | .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     |
| Pancreatic cancer, cases     | 116   | 111   | 109   | .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 1                      | 1.00  | 0.97  | 0.94  | .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     |
| Model 2                      | 1.00  | 0.96  | 0.93  | .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   | .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 1                      | 1.00  | 1.05  | 1.09  | .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  | 1.14  | .700     | 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    | .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 1                      | 1.00  | 0.96  | 1.07  | .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  | 1.39  | .352     | 1.00  | 1.13 (0.82-1.55) | 1.39 (1.01-1.90) | .493     | 1.00  | 1.03 (0.78-1.38) | 1.07 (0.79-1.44) | .883     |
| Biliary tract cancer, cases  | 113   | 104   | 113   | .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     |
| Model 1                      | 1.00  | 0.97  | 1.03  | .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  | 0.97  | .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    | .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     |
| Model 1                      | 1.00  | 1.26  | 1.27  | .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)
| Cancer type                              | Overall LCD score | Animal-based LCD score | Plant-based LCD score |
|-----------------------------------------|-------------------|------------------------|-----------------------|
|                                         | Q1 | Q3 | Q5 | P-trenda | Q1 | Q3 | Q5 | P-trenda | Q1 | Q3 | Q5 | P-trenda |
| Model 2                                 | 1.00 | 1.24 | 1.23 | .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, casesb                 | 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) | .999 | 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, casesb                   | 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.
intakes. One reported null associations with overall cancer and site-specific cancer incidence; the other suggested that an LCHP diet was linked to lower prostate cancer incidence. For mortality, a positive association has been found for animal-based LCD score and cancer mortality for pooling NHS and HPFS. In cohort studies of Swedish women or Japanese adults, 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 intake of animal products is related to a westernized dietary pattern, which favors a higher intake of animal products. According to the World Cancer Research Fund's Cancer Report, 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. 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. Similarly, dietary fiber has anti-inflammatory properties; some types could attenuate postprandial rises in blood glucose and insulin by reducing the rate of glucose absorption. 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 NOCs from red meat or processed meat are more carcinogenic to the rectum than the colon. Differences in rates of metabolism, fermentation, transit time, and expression of enzymes

### 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

| Cancer type | Overall LCD score | Q1 (2-5) | Q2 (9-11) | Q3 (14-16) | Q4 (19-22) | Q5 (24-28) | P-trenda |
|-------------|-------------------|---------|---------|---------|---------|---------|---------|
| 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.

aLinear trend across quintiles of LCD score was tested by entering the median values of each quintile into the Cox proportional hazards model.
and different morphology, are considered to be the reasons for the difference in the effect of a risk factor on the colon and rectum.\textsuperscript{31} Alternatively, it has been pointed out that an LCD with higher animal product consumption would increase the levels of cancer-promoting metabolites.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{37,38}; fresh fruits and vegetables are sources of ascorbic acid, which are linked to a reduction in stomach carcinogenesis.\textsuperscript{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.\textsuperscript{40} Previous studies in JPHC have suggested that a higher salt content in food is positively associated with GC risk,\textsuperscript{41} especially when typically consuming rice with salted foods.\textsuperscript{50} However, in our study, the group with low-carbohydrate intake (QS) 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.\textsuperscript{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.

\textit{H. pylori} is an independent factor responsible for GC, and 65\%-80\% of all GC cases were caused by \textit{H. pylori} infection.\textsuperscript{42} In our subpopulation, 92.2\% of GC cases were \textit{H. pylori} positive. Therefore, we could not assess the \textit{P}-value for interaction between LCD score and \textit{H. pylori} infection because GC cases without \textit{H. pylori} infections were limited. Analysis for the \textit{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 \textit{H. pylori} antibody-positive population (Table S1). We speculated that interactions between foods and \textit{H. pylori} might exist. Previous studies have revealed that a diet pattern high in sweets and carbohydrates was positively associated with prevalence of \textit{H. pylori} infection.\textsuperscript{43} The prevalence of \textit{H. pylori}-related gastric pre-cancerous lesions progressively increased with increased starchy vegetable intake and reduced fresh fruit intake.\textsuperscript{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 \textit{H. pylori} and other microorganisms.\textsuperscript{45,46} Protein-enriched foods are potent stimulants of gastric acid secretion.\textsuperscript{38} Therefore, for the \textit{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 \textit{H. pylori}. However, a similar protective association for plant-based LCD in the whole population was not observed in the \textit{H. pylori} antibody-positive population. Considering that the \textit{H. pylori} infection status could not be adjusted in the whole population analysis, residual confounding of \textit{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-\textit{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 \textit{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
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