Rice, bread, noodle and cereal intake and colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective Study (JPHC Study)

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Background: Colorectal cancer (CRC) incidence rate increased rapidly in Japan between the 1950s and 1990s. We examined the association between rice intake and CRC risk in comparison with bread, noodles and cereal among Japanese adults enrolled in the Japan Public Health Center-based prospective Study.

Methods: A total of 73,501 Japanese men and women were followed-up from 1995 to 1999 until the end of 2008 for an average of 11 years. During 801,937 person-years of follow-up, we identified 1276 incident cases of CRC. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of CRC for rice, noodle, bread and cereal intake were calculated by Cox proportional hazards model.

Results: Overall, no significant association was observed for the highest quartile of rice intake compared with the lowest and the risk of CRC and its subsites in men (HR, 0.77; 95% CI, 0.56–1.07) and women (HR, 1.10; 95% CI, 0.71–1.68). However, a non-significant inverse trend was observed between rice intake and rectal cancer in men. No clear patterns of association were observed in bread, noodle and cereal intake.

Conclusion: Our findings suggest that the consumption of rice does not have a substantial impact on the risk of CRC in the Japanese population.
form of white rice (Kenko Eijyo Joho Kenkyukai, 2009; Nanri et al., 2010; Science and Technology Agency, 2005; Uchida et al., 2010). There is also some, albeit limited, evidence from the 1970s suggesting large quantities of rice may increase the risk of CRC (Burkitt, 1971; Haenszel et al., 1973). However, the evidence for rice and CRC risk in the general population has been sparse. Therefore, we for the first time analysed a large-scale prospective population-based cohort to understand the association between CRC and rice intake in the Japanese population.

### MATERIALS AND METHODS

**Study population.** The Japan Public Health Center-based prospective Study (JPHC Study) is a 30-year on-going cohort study focusing on cancer, cardiovascular and other lifestyle-related diseases, consisting of ~140,000 Japanese citizens, aged 40–69 years at baseline (1990–1994), in 11 public health centres throughout Japan. The details of the study design have been described elsewhere (Tsugane and Sobue, 2001). Study participants responding to the 5-year follow-up questionnaire 1995–1999, aged 45–74 years were included in the present study. One public health centre area was excluded because cancer incidence information was not available. We started with a population-based cohort of 133,333 participants. We excluded 245 disqualified subjects, 11,583 who had died, moved out of the study area or were lost to follow-up before the starting point. From these, 98,505 responded enrolled in our analysis. Subjects with missing values for covariates were excluded (n = 17,021), resulting in a final sample of 73,501 men (n = 35,559) and women (n = 38,492).

**Dietary assessment.** In the validated FFQ (Ishihara et al., 2003; Sasaki et al., 2003; Ishihara et al., 2006; Nanri et al., 2010), participants were asked about the frequency of consumption of individual food items as well as representative sizes relative to standard portions. Details regarding carbohydrate-related food items collected in the JPHC Study were described previously (Nanri et al., 2010). Briefly, for rice (japonica rice; round and short grain), participants selected from nine options ranging from < 1 bowl per day to ≥ 10 bowls per day and rice-bowl portion size: small (110 g of rice), medium (140 g of rice) and large (170 g of rice).

**Follow-up and identification of CRC cases.** Subjects were followed for move-out, death and occurrence of cancer from the 5-year follow-up survey (around 1995 and 1998) through 31 December 2008.

We identified CRC incidence by hospital records and population-based cancer registries in the study areas. We coded CRC cases as C18-C20 according to the International Classification of Diseases for Oncology, third edition. We further divided CRC into colon (C18.0–C18.5 for proximal colon and C18.6–C18.7 for distal colon) and rectal (C19 and C20) cancer.

**Statistical analysis.** We excluded participants who had been diagnosed with or reported as having cancer before the starting point (n = 4086) or subjects with missing information for main exposure variables: that is, rice, bread, noodle intake (n = 1030) or who reported extreme total energy intakes (upper 2.5% or lower 2.5%; n = 4666) or missing data. A total of 88,722 participants were enrolled in our analysis. Subjects with missing values for covariates were excluded (n = 15,221), resulting in a final sample of 73,501 men (n = 34,559) and women (n = 38,492).

**Table 1. Age-adjusted characteristics of study participants at the 5-year follow-up survey according to quartiles of rice intake in the JPHC Study**

| Variable | Men (n = 34 559) | Women (n = 38 492) |
|----------|----------------|-------------------|
| Q1 (low) | Q2             | Q3                | Q4 (high) | P-value | Q1 (low) | Q2 | Q3 | Q4 (high) |
| Rice (g per day) | 0.0001 | 96 (0–122) | 143 (136–140) | 183 (147–183) | 244 (190–487) | <0.0001 |
| Rice (g per day) | median (range) | 122 (0–136) | 183 (137–183) | 244 (190–243) | 305 (273–592) |
| Rice (g per day) | 92 ± 0.45 | 176 ± 0.13 | 238 ± 0.14 | 331 ± 0.65 | <0.0001 | 90 ± 0.34 | 140 ± 0.05 | 183 ± 0.01 | 263 ± 0.80 | <0.0001 |
| Age (years) | 56.78 ± 7.90 | 57.00 ± 7.96 | 55.16 ± 7.06 | 55.56 ± 7.92 | <0.0001 | 55.89 ± 7.69 | 57.39 ± 8.73 | 56.80 ± 7.71 | 55.74 ± 7.10 | <0.0001 |
| BMI (kg·m⁻²) | 23.72 ± 0.03 | 23.66 ± 0.02 | 23.45 ± 0.04 | 23.42 ± 0.04 | <0.0001 | 23.37 ± 0.03 | 23.67 ± 0.04 | 23.51 ± 0.02 | 23.40 ± 0.06 | <0.0001 |
| Alcohol intake (%) | 74.71 | 72.18 | 70.97 | 49.83 | <0.0001 | 22.67 | 15.88 | 15.74 | 15.74 | <0.0001 |
| Current smoker (%) | 45.71 | 45.89 | 51.98 | 50.48 | <0.0001 | 7.10 | 4.60 | 4.57 | 5.34 | <0.0001 |
| METs (MET·h per day) | 31.57 ± 0.07 | 32.49 ± 0.05 | 33.68 ± 0.10 | 34.97 ± 0.11 | <0.0001 | 31.75 ± 0.05 | 32.22 ± 0.08 | 32.27 ± 0.05 | 32.83 ± 0.10 | <0.0001 |
| History of type 2 diabetes (%) | 10.00 | 10.06 | 6.97 | 5.64 | <0.0001 | 4.36 | 5.43 | 3.71 | 2.86 | <0.0001 |
| CRC screening (%) | 31.05 | 32.64 | 32.05 | 33.78 | NS | 29.93 | 33.20 | 34.54 | 30.37 | <0.0001 |
| Post-menopausal status (%) | — | — | — | — | — | 75.47 | 75.48 | 75.31 | 74.67 | NS |
| Hormone use (%) | — | — | — | — | — | 3.08 | 2.83 | 2.47 | 2.20 | <0.0001 |

**Dietary intake**

| Total energy (cal per day) | 1945.25 ± 6.45 | 2009.04 ± 4.81 | 2342.33 ± 8.00 | 2629.27 ± 8.54 | <0.0001 | 1732.93 ± 4.38 | 1882.57 ± 7.47 | 1948.50 ± 4.30 | 2210.65 ± 9.37 | <0.0001 |
| Bread (g per day) | 32 ± 0.49 | 21 ± 0.27 | 20 ± 0.45 | 16 ± 0.36 | <0.0001 | 41 ± 0.42 | 23 ± 0.41 | 23 ± 0.24 | 23 ± 0.63 | <0.0001 |
| Nooodles (g per day) | 131 ± 1.40 | 117 ± 0.91 | 116 ± 1.43 | 110 ± 1.51 | <0.0001 | 96 ± 0.81 | 91 ± 1.17 | 91 ± 0.69 | 94 ± 1.53 | NS |
| Cereals (g per day) | 285 ± 1.59 | 326 ± 0.99 | 385 ± 1.59 | 468 ± 1.77 | <0.0001 | 254 ± 0.96 | 284 ± 1.36 | 307 ± 0.79 | 392 ± 1.94 | <0.0001 |
| Red meat (g per day) | 49 ± 0.51 | 49 ± 0.35 | 48 ± 0.56 | 46 ± 0.60 | NS | 42 ± 0.33 | 44 ± 0.57 | 43 ± 0.32 | 41 ± 0.63 | NS |

**Abbreviations:** BMI = body mass index; CRC = colorectal cancer; JPHC = Japan Public Health Center-based; MET = metabolic equivalent task; NS = non-significant; PUFA = polyunsaturated fatty acid; Q = quartile. Values are age-adjusted mean ± s.e., unless stated otherwise. Alcohol consumption > 1 g ethanol per week; CRC screening included fecal occult blood test, barium enema or colonoscopy; hormone use, current use of exogenous female hormones (%). Subjects with missing data were excluded (BMI: n = 219); smoking status: n = 472; alcohol consumption: n = 668; MET: n = 2948; menstruation: n = 2898; hormone use: n = 2674; n = 98 (PUFA) total excluded: n = 15,221.
We calculated person-years of follow-up for each participant from the starting point to the date of CRC diagnosis, date of emigration from the study area, date of death or end of the follow-up (31 December 2008), whichever came first. Using Cox proportional hazards models, we calculated the risk for developing CRC and its anatomic subsites for rice, bread, noodle and cereal categories in quartiles and per 100 g increase by sex, with the lowest consumption category as the reference, adjusted for potential confounding variables (indicated in Tables 2 and 3). The median value of each quartile was included in the trend analysis. Covariates were included based on associations found in our previous studies on CRC. Dietary factors were adjusted by total energy using the residual method (Kipnis et al, 1993; Brown et al, 1994; Willett et al, 1997; Akhter et al, 2008). All analyses were performed with Stata SE 12.1 (StataCorp, College Station, TX, USA).

**RESULTS**

During 801,937 person-years of follow-up, we identified 1276 incident cases of CRC (777 for men and 499 for women) (Table 1). Age-adjusted CRC incidence ranged from 20.62 (highest quarter of rice) to 24.10 (lowest) in men and from 11.20 to 12.05 in women. Table 2 presents Hazard ratios (HRs) and 95% confidence intervals (CIs) for CRC incidence according to quartile of rice, bread, noodle and cereal intake among Japanese men and women. The multivariate HRs for the highest compared with the lowest quartile of rice in men was 0.77 (95% CI, 0.56–1.07). The trend analysis, analysed by scores, was not statistically significant. In women, no association was found for rice intake and CRC risk; however, a non-significant trend between increased cereal intake and the risk of CRC was found.

### Table 2. Hazard ratio (HR) and 95% CI of colorectal cancer according to quartiles of rice, bread, noodle and cereal intake (g per day) in the JPHC Study

|               | Median (g per day) | Range (g per day) | No. cases | Person-years | Incidence rate* | HR (95% CI) | P trend | Per 100 g | (95% CI) |
|---------------|-------------------|------------------|-----------|--------------|----------------|--------------|---------|-----------|----------|
| **Rice**      |                   |                  |           |              |                |              |         |           |          |
| Q1            | 122               | 0–136            | 217       | 90,336.74    | 24.10          | 1.00 (Reference) |         | 0.179     | 0.312    |
| Q2            | 183               | 137–183          | 338       | 161,548.73   | 21.40          | 0.88 (0.73–1.06) | (0.71–1.18) | 3.24      | (0.82–1.48) |
| Q3            | 244               | 190–243          | 128       | 62,110.34    | 22.89          | 0.91 (0.56–1.07) | (0.56–1.07) | 3.24      | (0.71–1.68) |
| Q4            | 305               | 273–592          | 94        | 52,997.71    | 20.62          | 0.77 (Reference) |         | 0.93 (0.82–1.04) | 1.11 (0.92–1.35) |
| **Bread**     |                   |                  |           |              |                |              |         |           |          |
| Q1            | 4                 | 0–4              | 326       | 138,252.72   | 24.67          | 1.00 (Reference) |         | 0.751     | 0.986    |
| Q2            | 13                | 6–11             | 194       | 91,057.57    | 23.18          | 0.93 (Reference) |         | 0.751     | 0.986    |
| Q3            | 19                | 15–30            | 114       | 61,917.40    | 20.30          | 0.94 (Reference) |         | 0.93 (0.78–1.23) | 1.06 (0.77–1.45) |
| Q4            | 60                | 45–720           | 143       | 75,765.81    | 19.69          | 0.98 (Reference) |         | 0.93 (0.78–1.23) | 1.06 (0.77–1.45) |
| **Noodle**    |                   |                  |           |              |                |              |         |           |          |
| Q1            | 33                | 0–45             | 210       | 106,032.54   | 19.98          | 1.00 (Reference) |         | 0.301     | 0.230    |
| Q2            | 68                | 45–82            | 170       | 73,397.31    | 23.97          | 1.02 (1.02–1.54) | (0.96–1.44) | 0.99 (0.78–1.28) | 1.05 (0.77–1.45) |
| Q3            | 114               | 82–144           | 203       | 97,248.08    | 22.99          | 1.11 (0.95–1.47) | (0.95–1.47) | 0.99 (0.77–1.28) | 1.05 (0.77–1.45) |
| Q4            | 224               | 144–2800         | 194       | 90,319.58    | 23.85          | 0.99 (Reference) |         | 0.301     | 0.230    |
| **Cereal**    |                   |                  |           |              |                |              |         |           |          |
| Q1            | 215               | 30–248           | 193       | 86,168.81    | 22.00          | 1.00 (Reference) |         | 0.99 (0.77–1.28) | 1.05 (0.77–1.45) |
| Q2            | 284               | 248–318          | 200       | 90,071.01    | 22.90          | 1.01 (Reference) |         | 0.99 (0.77–1.28) | 1.05 (0.77–1.45) |
| Q3            | 357               | 318–406          | 196       | 94,350.91    | 22.62          | 1.07 (Reference) |         | 0.99 (0.77–1.28) | 1.05 (0.77–1.45) |
| Q4            | 482               | 406–2983         | 188       | 96,402.78    | 23.36          | 0.97 (Reference) |         | 0.99 (0.77–1.28) | 1.05 (0.77–1.45) |

**Abbreviations:** CI = confidence interval; PHC = polyhydrocarbon; Q = quartile. Multivariate adjusted for age (years, continuous), area (10 PHCs), alcohol consumption (none; drinker: <150, 150–299, 300–449 or ≥450 g alcohol per week for men; none; drinker: <150 or ≥150 g per ethanol per week for women), smoking status (never, past, current: 1–19, 20–29, ≥30 cigarettes per day), BMI (<25; 25–26.9, 27–29.9, ≥30 kg m–2), quartile of metabolic equivalent tasks (h per day), history of diabetes mellitus (yes or no), colorectal screening (yes or no), menopausal status (yes or no, women only), use of exogenous female hormones (yes or no, women only), total energy intake (kcal per day, continuous), red meat intake (g per day), quartile and intakes (according to quartiles) of energy-adjusted calcium (mg per day), magnesium (mg per day), vitamin B6 (mg per day), vitamin B12 (µg per day), folate (µg per day), vitamin D (µg per day), n-3 polyunsaturated fatty acids (g per day) and fibre (g per day). Intake of rice, bread and noodles (g per day, quartile) were mutually adjusted for; energy-adjusted cereal intake was analysed in a separate model.

*Age-adjusted incidence rate.
Further stratified analyses showed site-specific results: colon, rectum, proximal and distal colon cancer (Table 3). We noted a non-significant inverse association between the quartiles of rice intake and the risk of rectal cancer (Table 3) in men. In women, a non-significant trend of risk increase by quartile of rice intake and proximal colon cancer (Table 3) was found but not in men. Distal colon cancer showed no association with rice in both sexes (Table 3).

A non-significant risk trend was observed for bread, noodle and cereal intake (see Supplementary Tables).

Sensitivity analyses were performed excluding cases from the first 3 years of observation; because of the outcome, dietary habits might have been influenced by preclinical symptoms; however, results were not substantially different.

**DISCUSSION**

This is the first population-based study on the association between rice intake and CRC in Japan. Overall, we found that rice intake was not associated with CRC in men and women. Results were similar for CRC subsites.

The effect of rice on CRC is inconclusive, especially in Asian populations, consuming a diet high in white rice. The Shanghai Women’s Health Study observed no association between rice intake and the risk of CRC (Li et al., 2011), which accords with the present result. In the case of Japan, descriptive data regarding the association between rice and CRC are inconsistent. Rice and CRC may be inversely associated as suggested by a decreasing trend of rice intake in Japan in recent decades (Kenko Eiyo Joho Kenkyukai, 2009) concurrent with increasing trends in CRC incidence. However, a positive link is implied by high mortality rates in prefectures where large amounts of rice are consumed (Tanaka et al., 2004; Ministry of Health Labour and Welfare, 2013a, b).

This inconsistency may confuse us to understand the association between rice intake and CRC.

Alternatively, rice intake may be a surrogate of a traditional Japanese diet and thus may represent specific dietary patterns associated with CRC risk. In particular, rice, not specifically white rice, may be an important source of dietary fibre, and a surrogate of starch. Fibre may have a protective role (Wakai et al., 2006, 2007; WCRF, 2007); however, results remain elusive. Refined carbohydrates are a possible aetiological factor related to CRC (Cleave, 1956) through two pathways: deficient fibre or bacterial changes – degradation of bile salts to carcinogens and induction of tumours (Burkitt, 1971). Starch may be important in the production of short-chain fatty acids and stool quality (Uchida et al., 2010), possibly affecting the colon and rectum. Starch may enhance colorectal carcinogenesis via hyperinsulinaemia, assumed to be a mechanism in obesity-related carcinogenesis (Giovannucci and Michaud, 2007). Resistant starch may be protective (Uchida et al., 2010).

Some studies indicated that diet-associated risk was more prominent in proximal (right) colon cancer in women (McMichael and Potter, 1983, 1985a, 1985b), whereas rectal cancer was more common among men (Wynder et al., 1969; Bonithon-Kopp and Benhamiche, 1999). Our non-significant results hint at an inverse trend between rice intake and rectal cancer among men, mirror the findings of a Japanese case–control study in the southern part of the country suggesting that rice consumption is inversely associated with distal colon and rectal cancers (Uchida et al., 2010). The difference in risk by sex has also been indicated in previous studies where rice intake was found to be protective regarding risk of colon cancer in men (Wynder et al., 1969; Correa, 1981). In-depth sex- and CRC subsite-specific research is needed to draw more precise conclusions.

The JPHC Study has several strengths such as including a large general population sample with high response and low loss-to-

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**Table 3. Hazard ratio (HR) and 95% CI of colon, rectal, proximal and distal colon cancer according to quartiles of rice intake (g per day) in the JPHC Study**

|                | Median (g per day) | Range (g per day) | No. cases | HR (95% CI) | Median (g per day) | Range (g per day) | No. cases | HR (95% CI) |
|----------------|-------------------|------------------|-----------|-------------|-------------------|------------------|-----------|-------------|
| **Proximal colon** |                   |                  |           |             |                   |                  |           |             |
| Q1              | 122               | 0–136            | 140       | 1.00 (Reference) | 77          | 1.00 (Reference) | 96        | 0–122       | 121        | 1.00 (Reference) |
| Q2              | 183               | 137–183          | 226       | 0.93 (0.74–1.17) | 112         | 0.79 (0.58–1.08) | 143       | 136–144     | 45         | 1.02 (0.71–1.46) |
| Q3              | 244               | 190–243          | 87        | 1.01 (0.73–1.39) | 41          | 0.76 (0.49–1.18) | 183       | 147–183     | 157        | 1.21 (0.90–1.61) |
| Q4              | 305               | 273–592          | 65        | 0.86 (0.58–1.32) | 29          | 0.61 (0.35–1.07) | 244       | 190–487     | 33         | 1.33 (0.82–2.16) |
| P-trend         | 0.685             | 0.085            |           |             | 0.156            | 0.726            |           |             |
| per 100 g       | 0.98 (0.84–1.14)  | 0.84 (0.69–1.03) |           |             | 1.16 (0.92–1.46) | 1.01 (0.72–1.43) |           |             |

| **Distal colon** |                   |                  |           |             |                   |                  |           |             |
| Q1              | 122               | 0–136            | 57        | 1.00 (Reference) | 76          | 1.00 (Reference) | 96        | 0–122       | 66         | 1.00 (Reference) |
| Q2              | 183               | 137–183          | 96        | 0.94 (0.66–1.34) | 114         | 0.92 (0.67–1.26) | 143       | 136–144     | 24         | 0.94 (0.57–1.53) |
| Q3              | 244               | 190–243          | 49        | 0.82 (0.53–1.45) | 119         | 0.74 (0.47–1.17) | 183       | 147–183     | 89         | 1.18 (0.80–1.73) |
| Q4              | 305               | 273–592          | 26        | 1.00 (0.55–1.81) | 49          | 0.77 (0.42–1.39) | 244       | 190–487     | 24         | 1.66 (0.90–3.05) |
| P-trend         | 0.903             | 0.737            |           |             | 0.139            | 0.480            |           |             |
| per 100 g       | 0.99 (0.79–1.24)  | 0.95 (0.77–1.17) |           |             | 1.30 (0.96–1.76) | 1.07 (0.72–1.57) |           |             |

Abbreviations: CI = confidence interval; JPHC Study = Japan Public Health Center-based prospective Study; Q = quartile. Multivariate adjusted for age (years, continuous), area (10 PHCs), alcohol consumption (none; drinker: <150, 150–299, 300–449 or ≥450 g ethanol per week for men; none; drinker: <150 or ≥150 g per ethanol per week for women), smoking status (never, past, current: 1–19, 20–29, ≥30 cigarettes per day), BMI (i.e. 25, 25–26.9, 27–29.9, ≥30 kg/m²), quartile of metabolic equivalent tasks (h per day), history of diabetes mellitus (yes or no) colorectal screening (yes or no), menopausal status (yes or no, women only), use of exogenous female hormones (yes or no, women only), total energy intake (kcal per day, continuous), red meat intake (g per day, quartile), bread, noodles (g per day, quartile) and intakes (according quartile) of energy-adjusted calcium (mg per day), magnesium (mg per day), vitamin B6 (mg per day), vitamin B12 (µg per day), folate (µg per day), vitamin D (µg per day), n-3 polyunsaturated fatty acids (g per day) and fibre (g per day). (see Supplementary Table for more detail).
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CONFLICT OF INTEREST

M directed the data, generated the tables and wrote the manuscript. MI* helped design the study and make comments regarding the intellectual content. JI and SS provided useful nutrition insights. TS, MI, TY and ST helped interpret the data in a meaningful way. NS and KS made substantial contributions strengthening the background and Discussion sections.

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APPENDIX

Members of the Japan Public Health Center-based Prospective Study (JPHC Study, principal investigator: S Tsugane) Group are: S Tsugane, S Sasazuki, M Iwasaki, N Sawada, T Shimazu, T Yamaji and T Hanaoka, National Cancer Center, Tokyo; T Kato, T Hira, S Koizumi, T Ito, H Kuriki, S Suzu, D Tamakoshi, A Ito, T Hirose, K Matsuo, T Hirose, K Kuriki, S Suzu, T Kato, T Hira, T Kanemitsu, Y Tajima (2006) Dietary risk factors for colon and rectal cancers: a comparative case-control study. J Epidemiol 16(3): 125–135.

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