Meat consumption and colorectal cancer risk in Japan: The Takayama study

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Compared with the abundant data from Western countries, evidence regarding meat consumption and colorectal cancer is limited in the Japanese population. We evaluated colorectal cancer risk in relation to meat consumption in a population-based prospective cohort study in Japan. Participants were 13,957 men and 16,374 women aged ≥35 years in September 1992. Meat intake, assessed with a validated food frequency questionnaire, was controlled for the total energy intake. The incidence of colorectal cancer was confirmed through regional population-based cancer registries and histological identification from colonoscopy in two main hospitals in the study area. From September 1992 to March 2008, 429 men and 343 women developed colorectal cancer. After adjustments for multiple confounders, a significantly increased relative risk of colorectal cancer was observed in the highest versus lowest quartile of the intake of total and red meat among men; the estimated hazard ratios were 1.36 (95% CI: 1.03, 1.79) for total meat (P for trend = 0.022), and 1.44 (95% CI: 1.10, 1.89) for red meat (P for trend = 0.009). A positive association between processed meat intake and colon cancer risk was also observed in men. There was no significant association between colorectal cancer and meat consumption in women. These results suggest that the intake of red and processed meat increases the risk of colorectal or colon cancer among Japanese men. Abstaining from excessive consumption of meat might be protective against developing colorectal cancer.

Colorectal cancer has high incidence and mortality worldwide.1,2 Among dietary factors related to the risk of colorectal cancer, the role of meat consumption has been widely examined by researchers. The World Cancer Research Fund and American Institute for Cancer Research have judged the intake of red and processed meat to be a “convincing” risk factor for colorectal cancer.2 In October 2015, based on published literature mainly on colorectal cancer, the International Agency for Research on Cancer (IARC) classified the consumption of red meat as probably carcinogenic to humans (Group 2A), and that of processed meat as carcinogenic to humans (Group 1).3 Thus, meat consumption is a source of increasing concern in public health.

In Japan, colorectal cancer is the second leading cause of cancer among both males and females.4,5 Compared with the abundant data from Western countries, evidence on meat consumption and colorectal cancer is limited among the Japanese population.6,7 Six prospective cohort studies have been conducted and obtained different results.8–13 Among them, only three studies on the incidence of colorectal cancer, including our previous report,8 have estimated the quantity of meat consumption using a validated food frequency questionnaire (FFQ), and considered several possible lifestyle confounders.8–10

In 2006, in the Takayama study, we reported an association between high consumption of processed meat and an increased risk of colon cancer identified by hospital records of colonoscopy among men after 8 years of follow-up.10 Since then, we have collected additional information from the cancer registry in the study area. In the present study, we evaluated colorectal cancer risk, including rectal cancer, in relation to meat consumption, using updated data files of colorectal cancer and an extended period of follow-up.

Materials and Methods
Participants and design. In September 1992, 36,990 residents of Takayama City, Gifu, Japan, aged ≥35 years who were not hospitalized were eligible to participate in the Takayama study. A total of 31,552 residents (85.3%) participated in the baseline survey and completed a self-administered questionnaire including an FFQ. The details of this population-based cohort study have been described elsewhere.14

Anthropometric characteristics, sociodemographic status, medical history, physical activity, smoking status, alcohol consumption, and regular diet were asked about in the baseline questionnaire. Reproductive characteristics including menopausal status and parity were included for women. Smokers were...
defined as people who had smoked a total of at least 20 packs of cigarettes in their life. We asked former and current smokers how long they had smoked. To assess physical activity both at work and at leisure, participants were asked the average time they spent on the following listed activities during the past year: strenuous sports, vigorous work, and moderate sports or work. The number of hours per week spent engaging in each activity was multiplied by the corresponding energy expenditure, expressed as metabolic equivalent of task (MET), and the product was taken as the physical activity score expressed as MET-h/week. The details of this approach including its validity are described elsewhere.\(^\text{15}\)

**Diet consumption.** Diet, including meat intake, was assessed using a semi-quantitative FFQ. Data were collected on the average frequency of consumption and the usual serving size for 169 food items and dishes during the past year. We defined red meat as beef and pork. Food items for red meat products included beef steak, pork steak, pork cutlet, grilled meat, grilled offal, and liver. Ham, sausage, bacon, and yakibuta (Chinese style roasted pork) were defined as processed meat. These items and some other dishes including meat products used as cooking ingredients were accounted for to obtain the estimates for meat intake. Total meat was defined as the sum of any kind of meat, including red meat, poultry, and processed meat. Each intake of nutrients, including red meat, poultry, and processed meat, was taken as a separate variable. The yield of meat was expressed as MET-h/week. The details of this approach including its validity are described elsewhere.\(^\text{15}\)

**Statistical analyses.** The values of the nutrients and foods consumed were controlled for the total energy intake using the residual method developed by Willett.\(^\text{19}\) Participants were categorized into quartile groups (Q1, Q2, Q3, or Q4) according to the distribution of their energy-adjusted intake of total meat, red meat, and processed meat.

Relative risks and 95% confidence intervals (CIs) for colorectal cancer were estimated for the quartile groups of each category of meat intake using a Cox proportional hazard model. The reference group was set as the lowest quartile (Q1) of each meat intake. The following covariates were included as potential confounders in the models: for men, age (years, continuous), height (quartiles), body mass index (quartiles), physical activity score (continuous), smoking status (never, past, current smoker who had smoked for \(\leq 30\) years, current smoker who had smoked for \(>30\) years), years of education (Q1, Q2, Q3, Q4), race (Japanese, non-Japanese), alcohol consumption (g/day), and energy-adjusted intake of dietary fiber (g/day), calcium (mg/day), and vitamin D (µg/day); for women, age, height, body mass index, physical activity score, smoking status (never, past, current smoker), years of education, history of aspirin use, alcohol consumption, menopausal status (premenopausal, postmenopausal), and energy-adjusted intake of dietary fiber, calcium, and vitamin D. Indicator terms were specifically created for missing data of categorical covariates. Tests for linear trend were conducted in the Cox model by treating meat intake as a continuous variable.

All analyses were conducted using the SAS program, version 9.4 (SAS Institute, Cary, NC). \(P\)-values were calculated by a two-sided test. A \(P\)-value less than 0.05 was considered statistically significant in all analyses.

**Results**

The characteristics of participants are shown in Table 1 as the mean (standard deviation) or the percentage of each category, according to the quartile groups of energy-adjusted total meat intake for each gender. Male and female participants in the higher quartile of total meat intake were younger and taller, and had attended school for a longer period at baseline. Women with a higher total meat intake tended to be premenopausal. Men and women among the lowest quartile of total meat intake had a higher level of alcohol consumption. Men in the lowest quartile and women in the highest quartile of total meat intake had a higher physical activity score.

In Table 2, after adjustments for multiple confounders, a significantly increased relative risk of colorectal cancer was observed in the highest intake group (Q4) of total meat and red meat in men; the estimated hazard ratios (HRs) were 1.36 (95% CI: 1.03, 1.79) for total meat, and 1.44 (95% CI: 1.10, 1.89) for red meat. The linear trends in these associations were statistically significant. A higher intake of total meat was significantly associated with a higher risk of colon cancer. Participants in the highest group of red meat intake had a significantly increased risk of rectal cancer. In addition,
After the addition of cancer registry data and the extension of follow-up to our previous report, this study revealed significant positive associations of total and red meat consumption with colorectal cancer risk in men. Higher intake of processed meat was associated with a higher risk of colon cancer in men.

Several supporting mechanisms have been proposed for the carcinogenic effects of meat. When meat is cooked at high temperatures by pan-frying, grilling, or barbecuing, heterocyclic aromatic amines and polycyclic aromatic hydrocarbons (PAHs), which are carcinogenic and mutagenic, are formed. Meat processing such as curing and smoking also produces PAHs and another carcinogenic N-nitroso compounds (NOCs). In the digestive tract, heme iron from red meat mediates the formation of NOCs, and the high fat content of red meat could also be a candidate for promoting tumorigenesis by enhancing the production of secondary bile acids by gut bacteria. In our study however, dietary intake of iron, animal fat, or saturated fat overall were not directly associated with colorectal cancer risk (data not shown).

The Japanese population is reported to consume a much lower amount of meat compared to Western populations. Furthermore, dietary habits, lifestyle, and genetic background in Japan are also different from those in Western countries. In a 2014 meta-analysis of six Japanese cohort studies and eight Japanese case-control studies on meat consumption and colorectal cancer incidence or mortality, Pham et al. reported that colorectal cancer risk had a statistically significant positive association with the consumption of red and processed meat, but not with total meat consumption. However, individual...
Table 2. Associations between meat consumption and colorectal cancer incidence among men

| Median intake (g) | No. of subjects | Person years | Colorectal cancer | Colon cancer | Rectal cancer |
|-------------------|-----------------|--------------|-------------------|-------------|--------------|
|                   | No. of cases    | No. of cases | RR†               | 95% CI      | RR†          | 95% CI      | RR†          | 95% CI      |
| Total meat‡       |                 |              |                   |             |              |             |              |             |
| Q1                | 110             | 72           | 1.00 Reference    |             | 38           | 1.00 Reference |
| Q2                | 107             | 65           | 1.08             | 0.76–1.52   | 42           | 1.26             | 0.80–1.97   |
| Q3                | 105             | 71           | 1.29             | 0.92–1.82   | 34           | 1.09             | 0.67–1.76   |
| Q4                | 107             | 68           | 1.36             | 0.96–1.93   | 39           | 1.34             | 0.84–2.14   |
| Trend P           |                 |              | 0.022             | 0.032       | 0.34         |              |             |
| Red meat‡         |                 |              |                   |             |              |             |              |             |
| Q1                | 105             | 68           | 1.00 Reference    |             | 37           | 1.00 Reference |
| Q2                | 105             | 70           | 1.23             | 0.88–1.74   | 35           | 1.07             | 0.66–1.71   |
| Q3                | 104             | 72           | 1.37             | 0.97–1.93   | 32           | 1.03             | 0.63–1.68   |
| Q4                | 115             | 66           | 1.31             | 0.92–1.86   | 49           | 1.65             | 1.06–2.58   |
| Trend P           |                 |              | 0.009             | 0.12        | 0.023        |              |             |
| Processed meat‡   |                 |              |                   |             |              |             |              |             |
| Q1                | 127             | 78           | 1.00 Reference    |             | 49           | 1.00 Reference |
| Q2                | 106             | 68           | 1.05             | 0.75–1.47   | 38           | 0.87             | 0.56–1.35   |
| Q3                | 92              | 58           | 1.00             | 0.70–1.42   | 34           | 0.85             | 0.54–1.35   |
| Q4                | 104             | 72           | 1.43             | 1.02–2.01   | 32           | 0.91             | 0.57–1.45   |
| Trend P           |                 |              | 0.32              | 0.17        | 0.86         |              |             |
| Excluding cases within 2 years | | | | | |
| Total meat‡       |                 |              |                   |             |              |             |              |             |
| Q1                | 99              | 63           | 1.00 Reference    |             | 36           | 1.00 Reference |
| Q2                | 97              | 59           | 1.13             | 0.79–1.63   | 38           | 1.18             | 0.74–1.89   |
| Q3                | 95              | 64           | 1.35             | 0.94–1.95   | 31           | 1.03             | 0.62–1.69   |
| Q4                | 102             | 65           | 1.50             | 1.05–2.16   | 37           | 1.31             | 0.81–2.12   |
| Trend P           |                 |              | 0.012             | 0.014       | 0.35         |              |             |
| Red meat‡         |                 |              |                   |             |              |             |              |             |
| Q1                | 94              | 60           | 1.00 Reference    |             | 34           | 1.00 Reference |
| Q2                | 98              | 64           | 1.29             | 0.90–1.85   | 34           | 1.11             | 0.69–1.81   |
| Q3                | 94              | 64           | 1.39             | 0.96–2.00   | 30           | 1.03             | 0.62–1.71   |
| Q4                | 107             | 63           | 1.43             | 0.99–2.05   | 44           | 1.57             | 0.99–2.50   |
| Trend P           |                 |              | 0.006             | 0.047       | 0.058        |              |             |
| Processed meat‡   |                 |              |                   |             |              |             |              |             |
| Q1                | 112             | 68           | 1.00 Reference    |             | 44           | 1.00 Reference |
| Q2                | 102             | 64           | 1.15             | 0.81–1.64   | 38           | 0.96             | 0.61–1.50   |
| Q3                | 84              | 55           | 1.11             | 0.76–1.62   | 29           | 0.80             | 0.49–1.31   |
| Q4                | 95              | 64           | 1.47             | 1.03–2.11   | 31           | 0.95             | 0.59–1.55   |
| Trend P           |                 |              | 0.24              | 0.14        | 0.98         |              |             |

†Estimated hazard ratio after adjustments for age, height (quartiles), body mass index (quartiles), physical activity score, smoking status (never, past, current smoker for 30 years or less, current smoker for 31 years or more), education years (≤8, 9–11, 12–14, ≥15 years), history of aspirin use (yes, no), alcohol consumption (g/day), and the intakes (quartiles) of total fiber, calcium, and vitamin D. ‡Meat consumption was adjusted for total energy intake by Willet method.

Prospective studies have failed to demonstrate a clear association between meat consumption and colorectal cancer. Three Japanese cohort studies on meat consumption and colorectal cancer mortality revealed no significant association. Firstly, the Miyagi cohort study revealed no significant association with total, red, or processed meat consumption. Secondly, the Japan Public Health Center-based prospective study reported that the HR of colon cancer for the highest versus lowest quintiles of red meat intake was 1.48 (95% CI: 1.01, 2.17, P for linear trend = 0.03) in women. Also, in men, the corresponding HR for total meat intake was 1.44 (95% CI: 1.06, 1.98, P for linear trend = 0.07). Thirdly, using updated data of the Takayama study, here we found significant positive associations of total and red meat consumption with colorectal cancer risk in men, in addition to an increased risk of colon cancer among men with high consumption of processed meat as observed previously. In women, there was no significant association of colorectal cancer with the intake of total, red, or processed meat, although the link between meat and colorectal cancer was not modified by sex. The effects of heme iron in red meat, which may be involved in carcinogenesis, might be weakened in women because of blood loss by menstruation, although the associations between meat consumption and colorectal cancer were not substantially different between premenopausal and postmenopausal women in our study (data not shown). Also, the lower intake of meat in women than men might have made it difficult to detect any association with colorectal cancer (mean in men and women: 74.3 and 59.0 g/day for total meat, 41.0 and 30.1 g/day for red meat, and 13.3 and 11.0 g/day for processed meat, respectively).
We conducted a meta-analysis of these six prospective studies and found that the pooled RRs of colorectal cancer in the highest category of consumption compared with the lowest category were recalculated as 1.22 (95% CI: 1.07, 1.39) for red meat, 1.09 (95% CI: 0.95, 1.26) for processed meat, and 1.07 (95% CI: 0.91, 1.26) for total meat, respectively, among all subjects. The increased risk of higher consumption of red meat was stronger in men (1.31 [95% CI: 1.10, 1.56]) than women (1.06 [95% CI: 0.81, 1.39]), and more prominent for colon cancer (1.29 [95% CI: 1.10, 1.52]) than rectal cancer (1.06 [95% CI: 0.81, 1.40]). Thus, the present study reinforced the positive association between red meat consumption and colorectal cancer in Japan, and also provided possible evidence for the difference in sex or subsites. In addition, the pooled RR did not show a significant association with processed meat, which has more robust evidence of carcinogenicity based on the international classification, but high consumption of processed meat is suggested to be associated with an increased risk of colon or colorectal cancer as observed in the Takayama study. Thus, more prospective studies are warranted to further assess these associations in Japan.

The strengths of our study include the prospective design, which minimalized recall bias, as well as the robust representation of the general population, good participation rate, long follow-up duration, and information on several confounders. Several potential limitations should be mentioned. The FFQ was designed to measure an individual’s relative intake of foods and nutrients, rather than absolute values. Some of values for dietary intakes we presented in the table may have been overestimated by the FFQ. In addition, the validity of
FFQ for total and red meat was low in men, which might have affected the results with colorectal cancer risk in this study. However, the observed association of total and red meat with colorectal cancer might have been underestimated because of a misclassification on dietary intake would likely have occurred non-differentially between participants with colorectal cancer and those without colorectal cancer. The exposure evaluation was performed only at baseline and changes in lifestyle patterns during the follow-up period were unknown. Although underlying diseases or preclinical signs may have affected lifestyle at baseline, the exclusion of cases during the first 2 years of follow-up did not substantially change the results. Despite considering several lifestyle and reproductive factors in the analyses, we could not fully exclude the possibility of residual confounders.

In conclusion, this prospective study in Japan demonstrated increased risk of colorectal cancer among men with higher intake of total and red meat. Higher intake of processed meat was associated with a higher risk of colon cancer in men. These results suggest that the intake of red and processed meat increases the risk of colorectal or colon cancer especially among men. In accordance with the assessment of the IARC, abstaining from overeating meat might be protective against developing colorectal cancer among the Japanese population.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

CI confidence intervals
FFQ food frequency questionnaire
IARC the international agency for research on cancer
MET metabolic equivalent
NOC N-nitroso compound
PAH polycyclic aromatic hydrocarbon

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