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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] 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.[8] 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.[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 was estimated using the Japanese Standard Table of Food Composition (5th revised and enlarged edition), published by the Japan Science and Technology Agency.[16] Both the validity and reproducibility of the questionnaire were previously reported to be reliable.[17] Spearman correlation coefficients between the FFQ and 12-day diet records kept over a 1-year period in men and women were 0.18 and 0.62 for total meat, 0.21 and 0.54 for red meat, and 0.58 and 0.69 for processed meat, respectively. Corresponding values were 0.44 and 0.53 for total energy, 0.78 and 0.73 for calcium, 0.55 and 0.36 for vitamin D, 0.63 and 0.60 for dietary fiber, and 0.72 and 0.64 for alcohol, respectively.

Colorectal cancer and follow-up. Participants were followed until the end of March 2008. At the baseline, 753 who were diagnosed with colorectal cancer before the baseline, and/or reported a positive history of any cancer and 535 who had a history of colorectal adenoma were excluded (there was some overlap). Consequently, 13 957 men and 16 374 women were included for analyses.

The cancer incidence was confirmed mainly through two regional population-based cancer registries in Gifu. We also gained some information on histological identification using colonoscopy from two main hospitals in Takayama city.[8,18] The causes of cancer were coded according to the International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10). Colorectal cancer was defined as the sum of code C18 (colon cancer) and code C19 and C20 (rectal cancer). When participants developed both colon and rectal cancer, the preceding cancer was assigned.

Migration data during the study period were obtained from the city residential registers or family registers. Colorectal cancer death was identified from death certificates provided by the Legal Affairs Bureau.

The endpoint of follow-up was determined by the earliest occurrence of one of the following events: a diagnosis of colorectal cancer, emigration from the study area, death, or the end of the study period. During the study period, 1767 persons (5.8%) moved away from the study area. For participants with who moved away on an unknown date (n = 238), their last date of residence that we could confirm was assigned as the endpoint of follow-up. Colorectal cancer developed in 429 men and 343 women, and 115 men and 107 women died of colorectal cancer. The mortality-to-incidence ratio for colorectal cancer was 0.29, and patients who were ascertained by death certificate-only registration were 6.2%, indicating satisfactory completeness of cancer information in this cohort. The ethical board of the Gifu University Graduate School of Medicine approved this study.

Statistical analyses. The values of the nutrients and foods consumed were controlled for the total energy intake using the residual method developed by Willett.[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 ≤30 years, current smoker who had smoked for ≥31 years), years of education (≤8, 9–11, 12–14, ≥15 years), history of aspirin use (yes, no), 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,

Table 1. Characteristics of study subjects at baseline

Total meat consumption†	Men (quartile)				Women (quartile)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
n	3490	3489	3489	3489	4094	4093	4094	4093
Age (years)	56.5 (11.8)	56.6 (12.5)	55.0 (12.8)	52.0 (11.7)	58.9 (12.7)	59.0 (13.6)	55.5 (13.4)	51.4 (11.5)
Height (cm)	164.1 (6.7)	163.9 (7.0)	164.7 (7.0)	165.6 (6.8)	151.3 (6.5)	151.1 (6.7)	152.2 (6.4)	153.2 (5.9)
Body mass index (kg/m^2)	22.6 (2.7)	22.3 (2.7)	22.4 (2.9)	22.7 (2.9)	22.0 (3.0)	21.9 (3.0)	22.0 (2.9)	22.1 (2.9)
Smoking status (never)	16.8%	17.6%	16.0%	16.1%	82.2%	83.6%	83.4%	80.8%
Physical activity score (METs-h/week)	29.9 (43.7)	26.5 (40.3)	25.5 (39.5)	27.6 (40.5)	17.7 (28.8)	17.9 (28.4)	18.3 (27.5)	22.0 (31.7)
Education years (≥12 years)	33.9%	37.3%	44.5%	51.9%	24.4%	26.8%	35.6%	44.9%
History of aspirin use (yes, no)	6.3%	7.4%	6.9%	7.8%	9.8%	8.3%	9.9%	12.0%
Alcohol consumption (g/day)	56.0 (51.5)	37.3 (37.0)	33.8 (33.2)	37.7 (37.0)	9.9 (22.2)	6.4 (13.7)	6.2 (13.4)	8.2 (16.2)
Total energy intake (kcal/day)	2968 (851)	2374 (726)	2300 (760)	2772 (960)	2460 (829)	1873 (641)	1852 (660)	2320 (814)
Total meat (g/day)	44.6 (27.1)	51.5 (28.9)	68.4 (31.2)	134.0 (66.8)	33.0 (24.4)	38.0 (24.3)	54.1 (25.8)	111.7 (55.6)
Red meat (g/day)	25.8 (16.5)	29.3 (16.9)	38.0 (19.0)	71.7 (40.3)	17.3 (13.4)	19.8 (13.4)	28.1 (14.5)	55.4 (30.3)
Processed meat (g/day)	8.2 (7.1)	9.0 (8.0)	11.9 (9.5)	24.4 (21.4)	6.6 (6.6)	7.1 (7.1)	9.7 (8.1)	20.9 (18.5)
Dietary fiber (g/day)	18.9 (10.7)	14.6 (7.7)	14.1 (6.8)	17.1 (8.3)	20.3 (11.1)	14.7 (7.5)	14.3 (7.0)	17.5 (8.4)
Calcium (mg/day)	883 (508)	654 (329)	633 (321)	752 (360)	899 (514)	641 (321)	613 (307)	756 (361)
Vitamin D (μg/day)	10.5 (7.5)	7.9 (5.5)	7.8 (5.0)	10.1 (6.4)	8.4 (5.9)	6.4 (4.2)	6.5 (4.2)	8.4 (5.0)
Menopausal status (pre)					29.1%	31.2%	42.6%	55.6%

Mean (standard deviation) or percentage. †Quartile groups according to the energy-adjusted intakes of total meat by Willet method.

participants in the highest group of processed meat intake had a significantly increased risk of colon cancer. In women, there was no significant association between colorectal cancer and total meat, red meat, or processed meat (Table 3).

To eliminate those who might have had colorectal cancer but who had not yet been diagnosed at baseline, we excluded 63 patients who were diagnosed with colorectal cancer in the first 2 years of follow-up and then re-analyzed the data. Although none of the results were substantially altered, the positive association between meat consumption and colon cancer in men seemed to be slightly strengthened (Table 2). Additionally, we observed a significant association between higher intake of red meat and increased risk of colon cancer (P for linear trend = 0.047).

When the association between seafood (fish and shellfish) consumption and colorectal cancer was evaluated similarly, the estimated HRs (95% CI) for colorectal cancer in the Q2, Q3, and Q4 *vs* the Q1 of seafood consumption were, respectively, 1.36 (0.99, 1.87), 1.16 (0.80, 1.67), and 1.29 (0.86, 1.94) for men, and 0.88 (0.62, 1.26), 1.17 (0.80, 1.72), and 1.48 (0.96, 2.27) for women.

Discussion

After the addition of cancer registry data and the extension of follow-up to our previous report,[8] 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.[20] 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.[21,22] Meat processing such as curing and smoking also produces PAHs and another carcinogenic N-nitroso compounds (NOCs).[22,23] In the digestive tract, heme iron from red meat mediates the formation of NOCs,[24,25] 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.[26] 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.[27] 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.[7] 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	RR†	95% CI	No. of cases	RR†	95% CI	No. of cases	RR†	95% CI
Total meat‡												
Q1	35	3490	46 270	110	1.00	Reference	72	1.00	Reference	38	1.00	Reference
Q2	61	3489	45 253	107	1.14	0.87–1.50	65	1.08	0.76–1.52	42	1.26	0.80–1.97
Q3	80	3489	45 223	105	1.22	0.92–1.61	71	1.29	0.92–1.82	34	1.09	0.67–1.76
Q4	114	3489	46 239	107	1.36	1.03–1.79	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	19	3490	45 951	105	1.00	Reference	68	1.00	Reference	37	1.00	Reference
Q2	33	3489	45 454	105	1.17	0.89–1.55	70	1.23	0.88–1.74	35	1.07	0.66–1.71
Q3	44	3489	45 400	104	1.24	0.94–1.65	72	1.37	0.97–1.93	32	1.03	0.63–1.68
Q4	64	3489	46 180	115	1.44	1.10–1.89	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	4	3490	46 197	127	1.00	Reference	78	1.00	Reference	49	1.00	Reference
Q2	9	3489	45 752	106	0.98	0.75–1.28	68	1.05	0.75–1.47	38	0.87	0.56–1.35
Q3	13	3489	44 833	92	0.94	0.71–1.25	58	1.00	0.70–1.42	34	0.85	0.54–1.35
Q4	23	3489	46 203	104	1.22	0.93–1.60	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	35	3481	46 272	99	1.00	Reference	63	1.00	Reference	36	1.00	Reference
Q2	61	3480	45 273	97	1.15	0.86–1.54	59	1.13	0.79–1.63	38	1.18	0.74–1.89
Q3	80	3480	45 221	95	1.23	0.92–1.65	64	1.35	0.94–1.95	31	1.03	0.62–1.69
Q4	114	3480	46 175	102	1.43	1.07–1.91	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	19	3481	45 967	94	1.00	Reference	60	1.00	Reference	34	1.00	Reference
Q2	33	3480	45 416	98	1.24	0.92–1.64	64	1.29	0.90–1.85	34	1.11	0.69–1.81
Q3	44	3480	45 404	94	1.25	0.93–1.68	64	1.39	0.96–2.00	30	1.03	0.62–1.71
Q4	64	3480	46 154	107	1.49	1.12–1.98	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	4	3481	46 237	112	1.00	Reference	68	1.00	Reference	44	1.00	Reference
Q2	9	3481	45 728	102	1.07	0.81–1.42	64	1.15	0.81–1.64	38	0.96	0.61–1.50
Q3	13	3479	44 784	84	0.98	0.73–1.33	55	1.11	0.76–1.62	29	0.80	0.49–1.31
Q4	23	3480	46 193	95	1.26	0.94–1.68	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.[11–13] Three other Japanese cohort studies have estimated the incidence of colorectal cancer.[8–10] Firstly, the Miyagi cohort study revealed no significant association with total, red, or processed meat consumption.[10] 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).[9] 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).

Table 3. Associations between meat consumption and colorectal cancer incidence among women

	Median intake (g)	No. of subjects	Person years	Colorectal cancer			Colon cancer			Rectal cancer		
				No. of cases	RR†	95% CI	No. of cases	RR†	95% CI	No. of cases	RR†	95% CI
Total meat‡												
Q1	26	4094	56 142	97	1.00	Reference	73	1.00	Reference	24	1.00	Reference
Q2	48	4093	55 387	101	1.12	0.84–1.49	72	1.04	0.74–1.45	29	1.35	0.78–2.34
Q3	64	4094	56 520	75	0.94	0.69–1.29	54	0.88	0.61–1.28	21	1.13	0.61–2.07
Q4	93	4093	58 632	70	1.01	0.74–1.40	45	0.88	0.60–1.30	25	1.43	0.80–2.56
Trend *P*					0.48			0.33			0.80	
Red meat‡												
Q1	12	4094	55 685	98	1.00	Reference	68	1.00	Reference	30	1.00	Reference
Q2	23	4093	55 271	97	1.07	0.80–1.42	77	1.21	0.86–1.69	20	0.75	0.42–1.33
Q3	32	4094	57 089	69	0.86	0.62–1.18	42	0.75	0.50–1.12	27	1.10	0.64–1.89
Q4	49	4093	58 636	79	1.07	0.79–1.46	57	1.13	0.79–1.64	22	0.95	0.54–1.68
Trend *P*					0.98			0.99			0.97	
Processed meat‡												
Q1	3	4094	56 692	100	1.00	Reference	74	1.00	Reference	26	1.00	Reference
Q2	8	4093	56 261	88	0.96	0.71–1.28	61	0.88	0.62–1.25	27	1.17	0.68–2.03
Q3	11	4094	55 763	81	0.98	0.72–1.34	63	1.00	0.70–1.44	18	0.90	0.48–1.69
Q4	19	4093	57 965	74	1.12	0.82–1.55	46	0.95	0.64–1.40	28	1.62	0.92–2.84
Trend *P*					0.95			0.25			0.10	
Excluding cases within 2 years												
Total meat‡												
Q1	26	4087	56 176	87	1.00	Reference	66	1.00	Reference	21	1.00	Reference
Q2	48	4087	55 452	89	1.09	0.80–1.47	61	0.97	0.68–1.39	28	1.46	0.82–2.59
Q3	64	4087	56 479	71	0.97	0.70–1.35	51	0.91	0.62–1.33	20	1.19	0.63–2.25
Q4	93	4086	58 540	69	1.09	0.78–1.51	44	0.93	0.62–1.38	25	1.59	0.87–2.91
Trend *P*					0.73			0.46			0.60	
Red meat‡												
Q1	12	4087	55 707	89	1.00	Reference	62	1.00	Reference	27	1.00	Reference
Q2	23	4087	55 326	86	1.03	0.76–1.39	66	1.13	0.79–1.61	20	0.81	0.45–1.46
Q3	32	4087	57 044	65	0.87	0.62–1.21	40	0.77	0.51–1.16	25	1.10	0.62–1.93
Q4	49	4086	58 569	76	1.10	0.80–1.51	54	1.14	0.78–1.67	22	1.02	0.57–1.84
Trend *P*					0.83			0.90			0.79	
Processed meat‡												
Q1	3	4087	56 698	92	1.00	Reference	68	1.00	Reference	24	1.00	Reference
Q2	8	4087	56 310	78	0.91	0.67–1.25	54	0.85	0.59–1.23	24	1.10	0.62–1.96
Q3	11	4087	55 750	74	0.95	0.69–1.32	56	0.96	0.65–1.40	18	0.94	0.50–1.79
Q4	19	4086	57 888	72	1.15	0.83–1.60	44	0.96	0.64–1.44	28	1.70	0.95–3.03
Trend *P*					0.85			0.31			0.062	

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

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 the

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 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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