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Meat subtypes and colorectal cancer risk: A pooled analysis of 6 cohort studies in Japan

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Abstract

Red meat and processed meat have been suggested to increase risk of colorectal cancer (CRC), especially colon cancer. However, it remains unclear whether these

Abbreviations: CI, confidence interval; CRC, colorectal cancer; DCC, distal colon cancer; HCAs, heterocyclic amines; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; JPHC-5y, Japan Public Health Center-based 5-year follow-up study; MIYAGI, Miyagi Cohort Study; NOC, N-nitroso compound; OHSAKI, Ohsaki National Health Insurance Cohort Study; PCC, proximal colon cancer; TAKAYAMA, Takayama Cohort Study.

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associations differ according to meat subtypes or colon subsites. The present study addressed this issue by undertaking a pooled analysis of large population-based cohort studies in Japan: 5 studies comprising 232 403 participants (5694 CRC cases) for analysis based on frequency of meat intake, and 2 studies comprising 123 635 participants (3550 CRC cases) for analysis based on intake quantity. Study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model and then pooled using the random effect model. Comparing the highest vs lowest quartile, beef intake was associated with an increased risk of colon cancer in women (pooled HR 1.20; 95% CI, 1.01-1.44) and distal colon cancer (DCC) risk in men (pooled HR 1.30; 95% CI, 1.05-1.61). Frequent intake of pork was associated with an increased risk of distal colon cancer in women (pooled HR 1.44; 95% CI, 1.10-1.87) for "3 times/wk or more" vs "less than 1 time/wk". Frequent intake of processed red meat was associated with an increased risk of colon cancer in women (pooled HR 1.39; 95% CI, 0.97-2.00; *P* trend = .04) for "almost every day" vs "less than 1 time/wk". No association was observed for chicken consumption. The present findings support that intake of beef, pork (women only), and processed red meat (women only) might be associated with a higher risk of colon (distal colon) cancer in Japanese.

KEYWORDS
colon cancer, pooled analysis, processed meat, rectal cancer, red meat subtype

1 | INTRODUCTION

Meat is one of the staple foods of the human diet, containing a good source of protein and several vitamins and minerals, and is a supplier of fat.[1] Although meat contains a high biological value of protein and essential micronutrients for a well-balanced diet,[1] high intake of meat, especially red and processed meat, has received increasing attention as a risk factor of CRC,[2] which is the third most common cancer worldwide.[3,4] In 2015, the IARC classified processed meat as carcinogenic to humans (Group 1) and red meat as probably carcinogenic to humans (Group 2A).[5] Although the panel of IARC concluded that red meat is a probable cause and processed meat is a convincing cause of colon cancer, no conclusion was drawn for rectal cancer.

Epidemiological evidence is, however, not entirely consistent. According to the systematic reviews and meta-analyses, some observed a significant positive association,[6-9] whereas others failed to confirm the associations of CRC with intake of red meat[10-12] and processed meat.[13] Given that the fat content and the total amount of heme iron, which is a potent carcinogenic agent,[14] vary according to red meat subtypes,[15,16] the risk of CRC and its subsites could vary across red meat subtypes. Epidemiological evidence on this issue is limited and conflicting. Specifically, a meta-analysis of 5 prospective studies found an increased risk for CRC or colon cancer with the intake of beef, but not of pork.[17] In contrast, a recent prospective study in the Swedish population reported that pork intake was associated with an increased risk of colon cancer, whereas beef intake was associated with a decreased risk of colon cancer.[18] Additionally, few studies examined meat-CRC risk association by subsites of the colon.[19,20]

In Japan, CRC is the third most common cancer type in men and the second in women.[21] In spite of westernization of lifestyle and diet,[22] the amount of red meat intake is still much lower than that of populations in Europe and America.[23,24] Based on a systematic review, we previously reported a positive association of high intake of red and processed meat with the moderate increased risk of CRC among Japanese individuals.[8] That study, however, did not use uniform classification and/or categorization of meat intake and did not control uniformly for potentially important confounding factors across the participating cohorts.

Here, we report a pooled analysis of the relationship between intake of meat and its subtypes with cancer risk of the colorectum and its subsites among 356 038 participants of 6 large population-based cohort studies in Japan, by using the same exposure category and adjusting for the same set of covariates across the studies. We hypothesized that higher intake of red meat and its subtypes (beef or pork) and processed meat is associated with increased risk of colon cancer.

2 | MATERIALS AND METHODS

2.1 | Study populations

The Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan has been undertaking pooled analyses using original data from major cohort studies to examine the

associations between lifestyle and major forms of cancers in Japanese individuals since 2006. To maintain high quality and comparability of data, the following inclusion criteria were defined as a priority for the present analysis: population-based cohort studies carried out in Japan, studies initiated between the mid-1980s and mid-1990s, studies with more than 30 000 participants, studies that obtained dietary information including meat intake in a baseline survey with a validated questionnaire, and studies that collected incidence data for CRC during a follow-up period. We identified the following 7 studies that met these criteria: (i) JPHC I;[25] (ii) JPHC II;[25] (iii) JACC;[26] (iv) MIYAGI;[27] (v) OHSAKI;[28] (vi) JPHC-5y;[25] and (vii) TAKAYAMA.[29] We excluded participants with missing information on meat intake and with a history of cancer at baseline in each cohort and those with any missing data on covariates, resulting in a sizable reduction in the number included in the analytic cohort. Each study was approved by the relevant institutional ethical review boards. The MIYAGI,[30] JPHC,[31] and TAKAYAMA[32] studies have already reported results on the associations between meat intake and CRC risk. For the present analysis, we reanalyzed the updated dataset for MIYAGI, JPHC, and TAKAYAMA studies. Selected characteristics of these cohort studies are shown in Table 1.

2.2 | Case ascertainment

Participants were followed from the baseline survey (JPHC I, 1990; JPHC II, 1993-1994; JACC, 1988-1990; MIYAGI, 1990; OHSAKI,1994; JPHC-5y, 1995-1999; TAKAYAMA, 1992) to the last follow-up data for cancer incidence (JPHC I, 2013; JPHC II, 2013; JACC, 2009; MIYAGI, 2007; OHSAKI, 2008; JPHC-5y, 2013; TAKAYAMA, 2008) in each study. Residence status in each study, including survival, was confirmed through the residential registry. Information on the cause of death was obtained from death certificates, coded according to the International Classification of Diseases, Tenth Revision.[33] Cases were coded according to ICD-O-3.[34] The study outcome was defined as incident CRC (ICD-O-3 codes C18.0-18.9, C19, and C20), colon cancer (ICD-O-3 codes C18.0-18.9), rectal cancer (ICD-O-3 codes C19.9, and C20.9), PCC (ICD-O-3 codes C18.0-18.5), and DCC (ICD-O-3, codes C18.6-18.7) diagnosed during the respective follow-up periods of each study.

2.3 | Assessment of meat intake

Meat intake was assessed using self-administered questionnaires. In 5 studies (JPHC I [baseline], JPHC II [baseline], JACC, MIYAGI, and OHSAKI), intake of beef, pork, processed meat (ham, sausage), and chicken was asked in terms of frequency and divided into 4 categories (<1 time/wk, 1-2 times/wk, 3-4 times/wk, or almost every day). In the other 2 studies (JPHC-5y and TAKAYAMA), where detailed dietary data are available, intake of unprocessed red meat (beef and pork), beef, pork, chicken, and processed meat (ham, sausage) was quantified and categorized according to quartiles within each cohort. Correlation coefficient between meat intake assessed by the questionnaire and the dietary record was as follows: beef, 0.43 in men and 0.53 in women; pork, 0.42 in men and 0.38 in women; processed meat, 0.45 in men and 0.35 in women; chicken, 0.20 in men and 0.27 in women for JPHC-5y[35]; and total meat, 0.18 in men and 0.62 in women; red meat, 0.21 in men and 0.54 in women; and processed meat, 0.58 in men and 0.69 in women for the TAKAYAMA study.[32] Dietary questionnaires used have been validated against dietary records in all participating cohorts except OHSAKI, which used the same questions on meat intake as MIYAGI.

2.4 | Statistical analysis

Person-years of follow-up were calculated from the date of baseline survey in each study until the date of CRC diagnosis, migration from the study area, death, or the end of follow-up, whichever came first. In each individual study, Cox proportional hazards models were used to estimate the HRs and 95% CIs of CRC or its subsites. The HRs were computed for the second through the highest category vs the lowest category of meat intake. All studies estimated 2 types of HRs: age (years, continuous) and area-adjusted (within each study for JPHC-I, JPHC-II, and JACC) HR and multivariate-adjusted HR. The multivariable-adjusted model included, in addition to age and area adjustments, history of diabetes (yes or no), body mass index (14 to <18.5, 18.5 to <22, 22 to <25, 25 to <30, or 30 to <40 kg/m^2), smoking status (for men, never smoker, past smoker, current smoker of 1-19, or ≥20 cigarettes/d; for women, never smoker, past smoker, or current smoker), alcohol drinking (for men, never/former drinker, occasional drinker of <once/wk, or current drinker of <23, 23 to <46, 46 to <69, 69 to <92, or ≥92 ethanol g/d; for women, never/former drinker, occasional drinker of <once/wk, or current drinker of <23 or ≥23 ethanol g/d), and nonoccupational physical activity (JPHC I and JPHC II, almost never, 1-3 d/mo, or ≥1 d/wk; JACC, MIYAGI, and OHSAKI, almost never or ≥1 h/wk; JPHC-5y, metabolic equivalent task-hour, quartiles; TAKAYAMA, no, 1-2, or ≥2 h/wk), log-transformed energy intake (continuous), calcium (quartiles), and fiber (quartiles). An indicator term for missing data was created for each covariate. We undertook a sensitivity analysis by excluding cases diagnosed within 3 years of baseline. The trend association was assessed by calculating the regression coefficient and its standard error of linear trend in each model, with ordinal numbers 0-3 assigned to the 4 categories of intake frequency or quartiles of meat intake. The proportional hazards assumption was examined for each study in a stepwise manner for the analyses of our primary hypothesis (for the association of red meat and its subtypes and processed meat with risk of colon cancer). In the first step, we tested the assumption by including a product term between each exposure of interest and follow-up period in the models (SAS; SAS Institute) or by using the Schoenfeld residuals method (Stata; Stata Corporation), depending on software available in each cohort. If the violation of the assumption was suggested ($P < .05$), we assessed graphically by plotting Schoenfeld residuals for each exposure of interest vs time. We confirmed that proportional hazards assumption was not violated in all except for the association of beef intake with CRC and colon cancer in women for the TAKAYAMA study. All the analyses were carried out using SAS or Stata statistical software.

TABLE 1 Characteristics of the participating Japanese cohort studies in the present pooled analyses

Study	Population	Age at baseline, y	Year of baseline survey	Population size	Response rate for baseline questionnaire, %	Method of follow-up	For the present pooled analysis						
							Age, y	Last follow-up time	Mean follow-up period, y	Size of cohort		No. of colorectal cancer cases	
										Men	Women	Men	Women
Analysis based on frequency of meat intake													
JPHC I	Residents of 5 public health center areas	40-59	1990	61 595	82	Cancer registry and death certificate	40-59	2013/12/31	20.0	19 789	21 176	823	554
JPHC II	Residents of 6 public health center areas	40-69	1993-1994	78 825	80	Cancer registry and death certificate	40-69	2013/12/31	16.6	27 524	30 216	936	602
JACC	Residents from 45 areas throughout Japan	40-79	1988-1990	110 585	83	Cancer registry (selected areas: 24) and death certificate	40-79	2009/12/31	15.6	29 221	41 381	717	596
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture	40-64	1990	47 605	92	Cancer registry and death certificate	40-64	2007/12/31	16.1	15 741	15 872	474	269
OHSAKI	Beneficiaries of National Health Insurance among residents of 14 municipalities in Miyagi Prefecture	40-79	1994	54 996	95	Cancer registry and death certificate	40-79	2008/03/31	10.9	15 502	15 981	478	245
Total				353 606						107 777	124 626	3428	2266
Analysis based on quantity of meat intake													
JPHC-5y	Residents of 10 public health centers	≥45-74	1995-1999	140 420	75	Cancer registry and death certificate	44-76	2013/12/31	15	43 448	49 388	1659	1090
TAKAYAMA	Residents of Takayama, Gifu Prefecture	≥35	1992	31 552	85	Cancer registry and death certificate	≥40	2008/03/31	13.5	14 224	16 575	449	352
Total				171 972						57 672	65 963	2108	1442

JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; MIYAGI, Miyagi Cohort Study; OHSAKI, Ohsaki National Health Insurance Cohort Study; TAKAYAMA, Takayama Study.

Resultant HRs from all of the 5 cohorts (JPHC I, JPHC II, JACC, MIYAGI, and OHSAKI) for frequency of meat intake and those from 2 cohorts (JPHC-5y and TAKAYAMA) for quantity of meat intake were each combined using a random effects model.[36] A study that had no cases for a category was not included in the pooled estimate for that category. For PCC and DCC, due to few or no cases in "almost every day" category, pooled estimate was obtained by combining "3-4 times/wk" and "almost every day" categories. Trend association was assessed by combining the regression coefficients and standard errors of linear trend across the participating cohorts by a random effects model. The extent of heterogeneity for each category was indicated by Cochran's *Q* statistic,[36] which was considered statistically significant when the *P* value was less than .10. The I^2 statistic was also reported to describe the percentage of total variation in the study-specific HRs, which was due to heterogeneity. We used the "metan" command in Stata for the meta-analysis.

3 | RESULTS

Analysis based on frequency of meat intake included 5 cohort studies comprising 232 403 participants and 5694 CRC cases for 1 815 617 person-years (average) of follow-up, whereas analysis based on quantity of meat intake included 2 cohort studies comprising 123 635 participants and 3550 CRC cases for 903 087 person-years (average) of follow-up (Table 1).

In the analyses of frequency of meat intake, we found no statistically significant associations of any type of meat with cancer risk of colorectum and its subsites in men (Table 2 and Table S1). In women (Table 3), processed red meat was significantly associated with an increased risk of CRC: the multivariable-adjusted HR for "almost every day" vs "<1 time/wk" was 1.33 (95% CI, 1.001-1.76; *P* trend = .12). The association was somewhat strengthened after excluding cases diagnosed within 3 years of the baseline (HR, 1.42; 95% CI, 1.04-1.96; *P* trend = .18) (Table S2). This association was observed only for colon cancer: multivariable-adjusted HR for "almost every day" vs "<1 time/wk" was 1.39 (95% CI, 0.97-2.00; *P* trend = .04) but not for rectal cancer. By combining the category of "3-4 times/wk" and "almost every day" in the colon subsite analysis, beef intake was associated with increased risk of DCC in the age- and area-adjusted model: pooled HR for "3-4 times/wk or more" vs "<1 time/wk" was 1.48 (95% CI, 1.03-2.11). This association was attenuated and became statistically nonsignificant after adjusting for all the potential confounding factors. Frequent pork intake was associated with an increased risk of DCC: the multivariable-adjusted HR for "3-4 times/wk or more" vs "<1 time/wk" was 1.44 (95% CI, 1.10-1.87; *P* trend = .07). Additionally, a weak, albeit not significant, positive association was found for processed red meat and DCC risk: the multivariable-adjusted HR for "3-4 times/wk or more" vs "<1 time/wk" was 1.30 (95% CI, 0.99-1.71). We also noticed that, after excluding cases diagnosed within 3 years of the baseline, chicken intake was associated with a decreased risk of CRC (pooled HR for "almost every day" vs "<1 time/wk" was 1.04 [95% CI, 0.66-1.63; *P* trend = .03]) or PCC (pooled HR for "3-4 times/wk or more" vs "<1 time/wk" was 0.71 [95% CI, 0.55-0.91; *P* trend = .01]) (Table S2).

As regards quantity-based analysis in men (Table 4), beef intake was significantly and positively associated with risk of DCC in men: the multivariable-adjusted HR in the highest vs lowest quartile of beef intake was 1.30 (95% CI, 1.05-1.61; *P*-trend = .02). The result was virtually unchanged after excluding cases diagnosed within 3 years of the baseline (HR, 1.29; 95% CI, 1.03-1.61; *P* trend = .04) (Table S3). In women (Tables 5 and S4), colon cancer was significantly and positively associated with beef intake: the multivariable-adjusted HR for the highest vs lowest quartile of beef intake was 1.20 (95% CI, 1.01-1.44; *P*-trend = .11). A similar association was found for colon cancer when beef intake was treated as a continuous variable: the multivariable-adjusted HR for 100-g increase of beef intake was 1.60 (95% CI, 1.04-2.46). However, no association was observed for PCC and DCC with any type of meat intake. We undertook a sensitivity analysis after excluding the TAKAYAMA study, in which Cox proportional hazards assumption was violated in women for the association of beef intake with CRC and colon cancer, and found a similar association (the multivariable-adjusted HR for the highest vs lowest quartile of beef intake was 1.11 [95% CI, 0.93-1.33] for CRC and 1.23 [95% CI, 1.00-1.52] for colon cancer).

4 | DISCUSSION

In this pooled analysis involving 356 038 participants and 9244 incident cases of CRC from 6 large-scale population-based cohort studies in Japan, higher intake of total red meat was not significantly associated with an increased risk of CRC and its subsites in both men and women. In the analysis for each subtype of red meat, we found a significant positive association between beef intake (quantity) and risk for colon cancer among women and risk for DCC among men and pork intake (frequency) and risk for DCC in women. We observed that the frequent intake of processed red meat was associated with an increased risk for CRC or colon cancer among women. There was no association for chicken.

Contrary to our prior expectation, total intake of red meat was not appreciably associated with CRC and its subsites. In an analysis by specific meat based on quantitative intake estimate, we found a significantly increased risk of cancer of the colon (women) and distal colon (men) associated with high beef intake, and results based on frequency of meat intake were also suggestive of the beef-colon cancer association in women. As regards pork intake, there was a significantly increased risk of DCC associated with its frequent intake ("3-4 times/wk or more") in women, whereas no such elevation was observed in the highest quartile of meat intake in both sexes. This seemingly more consistent association with beef than with pork agrees with the results of a meta-analysis,[17] showing an increased risk of colon cancer associated with high intake of beef, but not with pork. Accumulating evidence from experimental studies indicates that heme iron plays a

TABLE 2 Pooled multivariate hazard ratios and 95% confidence intervals[a] for the association between meat consumption (frequency) and colorectal cancer in men

Meat types	Meat intake, frequency				*P* for trend	Heterogeneity[c] *P*, I^2 (%)
	<1 time/wk	1-2 times/wk	3-4 times/wk[b]	Almost every day		
	Colorectal cancer					
Beef	1.00 (Ref.)	1.02 (0.93-1.11)	0.99 (0.78-1.27)	1.05 (0.68-1.63)	.99	.89, 0.0
Pork	1.00 (Ref.)	1.05 (0.95-1.16)	0.99 (0.88-1.11)	0.98 (0.77-1.26)	.71	.80, 0.0
Processed red meat	1.00 (Ref.)	0.93 (0.85-1.01)	0.90 (0.79-1.02)	1.13 (0.91-1.41)	.36	.55, 0.0
Chicken	1.00 (Ref.)	0.95 (0.82-1.09)	0.97 (0.80-1.17)	1.01 (0.72-1.41)	.59	.39, 3.4
	Colon cancer					
Beef	1.00 (Ref.)	1.00 (0.88-1.14)	0.98 (0.78-1.24)	1.10 (0.61-1.97)	.68	.61, 0.0
Pork	1.00 (Ref.)	1.10 (0.98-1.23)	1.03 (0.89-1.20)	0.99 (0.68-1.43)	.87	.27, 23.0
Processed red meat	1.00 (Ref.)	0.93 (0.83-1.03)	0.93 (0.79-1.10)	1.18 (0.78-1.79)	.78	.07, 54.6
Chicken	1.00 (Ref.)	0.95 (0.81-1.10)	1.00 (0.76-1.32)	0.80 (0.51-1.25)	.66	.95, 0.0
	Rectal cancer					
Beef	1.00 (Ref.)	1.04 (0.89-1.21)	1.01 (0.76-1.33)	1.32 (0.68-2.56)	.59	.94, 0.0
Pork	1.00 (Ref.)	0.96 (0.79-1.16)	0.93 (0.74-1.17)	1.05 (0.72-1.53)	.74	.72, 0.0
Processed red meat	1.00 (Ref.)	0.93 (0.77-1.13)	0.86 (0.69-1.07)	1.11 (0.77-1.62)	.39	.75, 0.0
Chicken	1.00 (Ref.)	0.93 (0.81-1.07)	0.91 (0.74-1.13)	1.47 (0.92-2.36)	.76	.47, 0.0
	Proximal colon cancer					
Beef	1.00 (Ref.)	0.98 (0.77-1.25)	1.02 (0.75-1.37)		.78	.48, 0.0
Pork	1.00 (Ref.)	1.05 (0.88-1.25)	1.05 (0.86-1.28)		.70	.88, 0.0
Processed red meat	1.00 (Ref.)	1.05 (0.89-1.24)	1.07 (0.86-1.33)		.67	.84, 0.0
Chicken	1.00 (Ref.)	1.02 (0.87-1.21)	1.01 (0.74-1.38)		.83	.12, 36.9
	Distal colon cancer					
Beef	1.00 (Ref.)	0.98 (0.81-1.19)	1.15 (0.87-1.51)		.74	.65, 0.0
Pork	1.00 (Ref.)	1.22 (0.89-1.69)	1.02 (0.84-1.25)		.79	.66, 0.0
Processed red meat	1.00 (Ref.)	0.82 (0.71-0.96)	0.98 (0.75-1.27)		.42	.12, 36.5
Chicken	1.00 (Ref.)	0.88 (0.69-1.12)	0.91 (0.74-1.13)		.38	.76, 0.0

[a]Adjusted for age (years, continuous), area, history of diabetes (yes or no), body mass index (14 to <18.5, 18.5 to <22, 22 to <25, 25 to <30, or 30 to <40 kg/m^2), smoking status (never smoker, past smoker, current smoker of 1-19, or ≥20 cigarettes/d), alcohol drinking (never/former drinker, occasional drinker of <once/wk, or current drinker of <23, 23 to <46, 46 to <69, 69 to <92, or ≥92 ethanol g/d), nonoccupational physical activity (Japan Public Health Center-based Prospective Study I and II, almost never, 1-3 d/mo, or ≥1 d/wk; Japan Collaborative Cohort Study, Miyagi Cohort Study, and Ohsaki National Health Insurance Cohort Study, almost never or ≥1 h/wk), log-transformed energy intake (continuous), calcium (quartiles), and fiber (quartiles).
[b]Pooled estimate was obtained by combining "3-4 times/wk" and "almost every day" categories for proximal and distal colon cancer.
[c]For the highest category.
Ref., reference.
HRs values in bold show statistical significance.

crucial role in colon carcinogenesis.[14,37,38] The heme iron stimulates endogenous formation of NOCs,[37] which increases the proliferation of the colonic epithelium and the production of cytotoxic aldehydes by the process of lipid peroxidation.[37,38] A meta-analysis of prospective studies also provided data to support a role of heme iron in colon carcinogenesis.[39] The higher amount of heme iron in beef compared with other meat[15] could partly account for the more consistent association between beef intake and colon cancer risk.

In the analyses by colon subsite, we observed an increased risk of cancer associated with red meat type (beef intake in men and pork intake in women) for DCC but not for PCC. This differential association by colon subsite agrees with findings of a meta-analysis of 7 prospective studies, which reported a stronger association of DCC than PCC with red meat intake.[40] Such differential association by colon subsite has been ascribed to different exposure levels to potential carcinogens. Specifically, the concentrations of bile acid

TABLE 3 Pooled multivariate hazard ratios and 95% confidence intervals[a] for the association between meat consumption (frequency) and colorectal cancer in women

Meat types	Meat intake in frequency				*P* for trend	Heterogeneity[c] *P*, I^2 (%)
	<1 time/wk	1-2 times/wk	3-4 times/wk[b]	Almost every day		
	Colorectal cancer					
Beef	1.00 (Ref.)	0.99 (0.89-1.11)	1.07 (0.88-1.31)	1.19 (0.67-2.12)	.78	.51, 0.0
Pork	1.00 (Ref.)	1.06 (0.91-1.24)	1.12 (0.98-1.29)	1.03 (0.75-1.41)	.44	.46, 0.0
Processed red meat	1.00 (Ref.)	1.06 (0.95-1.17)	1.11 (0.94-1.30)	**1.33 (1.001-1.76)**	.12	.40, 1.3
Chicken	1.00 (Ref.)	0.94 (0.85-1.05)	0.89 (0.76-1.03)	1.01 (0.68-1.49)	.07	.49, 0.0
	Colon cancer					
Beef	1.00 (Ref.)	0.96 (0.84-1.09)	1.03 (0.82-1.31)	1.16 (0.55-2.47)	.66	.42, 0.0
Pork	1.00 (Ref.)	1.02 (0.89-1.18)	1.16 (0.99-1.37)	0.91 (0.62-1.35)	.45	.57, 0.0
Processed red meat	1.00 (Ref.)	1.05 (0.93-1.19)	1.17 (0.98-1.40)	1.39 (0.97-2.00)	**.04**	.34, 12.3
Chicken	1.00 (Ref.)	0.96 (0.85-1.08)	1.00 (0.76-1.32)	0.98 (0.54-1.75)	.20	.30, 17.8
	Rectal cancer					
Beef	1.00 (Ref.)	1.10 (0.89-1.35)	1.23 (0.83-1.80)	2.12 (0.86-5.18)	.19	.99, 0.0
Pork	1.00 (Ref.)	1.10 (0.90-1.34)	1.04 (0.80-1.35)	1.38 (0.81-2.35)	.78	.76, 0.0
Processed red meat	1.00 (Ref.)	1.07 (0.89-1.29)	0.98 (0.63-1.53)	1.17 (0.69-2.00)	.75	.92, 0.0
Chicken	1.00 (Ref.)	0.91 (0.72-1.15)	0.89 (0.62-1.27)	1.43 (0.56-3.70)	.43	.19, 37.6
	Proximal colon cancer					
Beef	1.00 (Ref.)	0.94 (0.79-1.13)	1.13 (0.83-1.53)		.77	.65, 0.0
Pork	1.00 (Ref.)	0.94 (0.79-1.11)	0.98 (0.80-1.19)		.63	.81, 0.0
Processed red meat	1.00 (Ref.)	1.05 (0.89-1.24)	1.20 (0.87-1.65)		.54	.05, 48.4
Chicken	1.00 (Ref.)	0.96 (0.82-1.13)	**0.74 (0.56-0.97)**		.05	.30, 16.2
	Distal colon cancer					
Beef	1.00 (Ref.)	1.07 (0.85-1.33)	1.31 (0.90-1.91)		.53	.65, 0.0
Pork	1.00 (Ref.)	1.29 (0.97-1.73)	**1.44 (1.10-1.87)**		.07	.88, 0.0
Processed red meat	1.00 (Ref.)	1.11 (0.84-1.47)	1.30 (0.99-1.71)		.15	.98, 0.0
Chicken	1.00 (Ref.)	0.96 (0.78-1.20)	1.25 (0.94-1.65)		.61	.89, 0.0

[a]Adjusted for age (years, continuous), area, history of diabetes (yes or no), body mass index (14 to <18.5, 18.5 to <22, 22 to <25, 25 to <30, or 30 to <40 kg/m^2), smoking status (never smoker, past smoker, or current smoker), alcohol drinking (never/former drinker, occasional drinker of <once/wk, or current drinker of <23 or ≥23 ethanol g/d), non-occupational physical activity (Japan Public Health Center-based Prospective Study I and II, almost never, 1-3 d/mo, or ≥1 d/wk; Japan Collaborative Cohort Study, Miyagi Cohort Study, and Ohsaki National Health Insurance Cohort Study, almost never or ≥1 h/wk), log-transformed energy intake (continuous), calcium (quartiles), and fiber (quartiles).
[b]Pooled estimate was obtained by combining "3-4 times/wk" and "almost every day" categories for proximal and distal colon cancer.
[c]For the highest category.
Ref., reference.
HRs values in bold show statistical significance.

metabolites are higher in the right than in the left side of the colon, whereas those of a marker of exposure to potentially carcinogenic NOCs are higher in the distal than in the proximal colonic DNA of CRC patients.[41,42] Animal studies show that endogenous N-nitrosation in the colon is dependent on the gut flora[43] and is most efficient at neutral pH.[44] Given the higher proportion of bacteria and pH in the distal colon than in the proximal colon,[45] the production of NOCs might be higher in the distal colon.

We found an increased risk of CRC or colon cancer with the frequent intake (almost every day) of processed red meat and risk in women but not in men. Accumulating evidence from meta-analyses consistently reported an increased risk of CRC with higher intake of processed red meat,[7,19,46] although these studies did not present the association by sex. Our findings were also compatible with a recent meta-analysis of 2 large cohorts (the Nurses' Health Study and Health Professional Follow-Up Study), which reported

TABLE 4 Pooled multivariate hazard ratios and 95% confidence intervals for the association between meat consumption (quantity) and colorectal cancer in men

Meat types	Meat intake in quantity				*P* for trend	Heterogeneity *P*, I^2 (%)	As continuous variable
	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)			
	Colorectal cancer						
Unprocessed red meat	1.00 (Reference)	0.99 (0.88-1.11)	1.05 (0.93-1.18)	1.13 (0.76-1.68)	0.51	.01, 85.8	1.19 (0.75-1.89)
Beef	1.00 (Reference)	1.06 (0.88-1.27)	1.05 (0.93-1.18)	1.08 (0.93-1.26)	.31	.26, 21.7	1.20 (0.70-2.05)
Pork	1.00 (Reference)	0.94 (0.83-1.07)	0.99 (0.88-1.11)	1.11 (0.82-1.49)	.46	.04, 75.4	1.39 (0.62-3.10)
Processed red meat	1.00 (Reference)	0.90 (0.80-1.02)	0.90 (0.79-1.01)	1.00 (0.76-1.32)	.94	.07, 69.9	1.00 (0.76-1.31)
Chicken	1.00 (Reference)	1.02 (0.90-1.15)	0.89 (0.79-1.01)	1.03 (0.90-1.19)	.84	.28, 15.9	1.01 (0.67-1.52)
	Colon cancer						
Unprocessed red meat	1.00 (Reference)	1.02 (0.88-1.18)	1.04 (0.84-1.27)	1.05 (0.78-1.41)	.73	.11, 60.7	1.07 (0.79-1.44)
Beef	1.00 (Reference)	1.12 (0.86-1.45)	1.06 (0.91-1.23)	1.06 (0.92-1.24)	.49	.54, 0.0	0.97 (0.70-1.35)
Pork	1.00 (Reference)	0.89 (0.76-1.03)	0.99 (0.85-1.14)	1.05 (0.80-1.38)	.60	.13, 57.3	1.24 (0.64-2.40)
Processed red meat	1.00 (Reference)	0.90 (0.78-1.05)	0.92 (0.79-1.07)	1.09 (0.78-1.52)	.65	.07, 70.5	1.13 (0.85-1.48)
Chicken	1.00 (Reference)	1.06 (0.92-1.23)	0.93 (0.80-1.08)	1.08 (0.88-1.33)	.87	.22, 34.6	1.27 (0.78-2.08)
	Rectal cancer						
Unprocessed red meat	1.00 (Reference)	0.90 (0.73-1.11)	1.04 (0.85-1.28)	1.21 (0.67-2.18)	.42	.02, 82.5	1.30 (0.64-2.65)
Beef	1.00 (Reference)	0.97 (0.79-1.20)	0.97 (0.78-1.20)	1.08 (0.83-1.41)	.56	.25, 26.1	1.49 (0.57-3.91)
Pork	1.00 (Reference)	1.08 (0.88-1.32)	0.93 (0.75-1.16)	1.16 (0.88-1.55)	.50	.22, 33.6	1.45 (0.50-4.18)
Processed red meat	1.00 (Reference)	0.88 (0.72-1.08)	0.83 (0.67-1.02)	0.87 (0.70-1.08)	.14	.71, 0.0	0.84 (0.54-1.30)
Chicken	1.00 (Reference)	0.90 (0.74-1.10)	0.83 (0.67-1.03)	0.96 (0.78-1.18)	.53	.85, 0.0	0.61 (0.32-1.19)
	Proximal colon cancer						
Unprocessed red meat	1.00 (Reference)	0.93 (0.74-1.16)	0.87 (0.69-1.10)	0.86 (0.64-1.16)	.13	.27, 17.6	0.80 (0.61-1.05)
Beef	1.00 (Reference)	0.91 (0.73-1.14)	0.85 (0.62-1.15)	0.80 (0.63-1.01)	.05	.88, 0.0	0.61 (0.35-1.07)
Pork	1.00 (Reference)	0.69 (0.43-1.12)	0.84 (0.65-1.10)	0.98 (0.77-1.25)	.88	.31, 2.9	1.15 (0.42-3.16)
Processed red meat	1.00 (Reference)	1.01 (0.81-1.27)	0.98 (0.78-1.24)	1.09 (0.63-1.90)	.76	.08, 67.6	1.03 (0.66-1.61)
Chicken	1.00 (Reference)	1.16 (0.92-1.45)	1.07 (0.85-1.35)	1.00 (0.79-1.27)	.41	.59, 0.0	1.54 (0.83-2.87)
	Distal colon cancer						
Unprocessed red meat	1.00 (Reference)	1.11 (0.91-1.36)	1.13 (0.88-1.45)	1.10 (0.88-1.36)	.42	.55, 0.0	1.17 (0.93-1.46)
Beef	1.00 (Reference)	1.21 (0.95-1.54)	1.26 (1.01-1.55)	**1.30 (1.05-1.61)**	**0.02**	.76, 0.0	1.31 (0.86-1.99)
Pork	1.00 (Reference)	1.00 (0.74-1.35)	1.04 (0.85-1.26)	0.98 (0.80-1.21)	.94	.63, 0.0	1.14 (0.85-1.53)
Processed red meat	1.00 (Reference)	0.58 (0.70-1.04)	0.86 (0.70-1.05)	1.13 (0.75-1.71)	.60	.09, 65.3	1.21 (0.69-2.13)
Chicken	1.00 (Reference)	1.06 (0.86-1.29)	0.88 (0.71-1.09)	1.16 (0.82-1.62)	.68	.16, 48.5	1.03 (0.57-1.87)

[a]Adjusted for age (years, continuous), area, history of diabetes (yes or no), body mass index (14 to <18.5, 18.5 to <22, 22 to <25, 25 to <30, or 30 to <40 kg/m^2), smoking status (never smoker, past smoker, current smoker of 1–19, or ≥20 cigarettes/d), alcohol drinking (never/former drinker, occasional drinker of <once/week, or current drinker of <23, 23 to <46, 46 to <69, 69 to <92, or ≥92 ethanol g/d), non-occupational physical activity (JPHC-5y, metabolic equivalent task-hours, quartiles; TAKAYAMA, no, 1–2, or ≥2 h/wk), log-transformed energy intake (continuous), calcium (quartiles), and fiber (quartiles).

[b]For the highest category.

[c]Per 100 g of unprocessed red meat, beef, pork, or chicken and per 50 g of processed meat.

Ref., reference.

HRs values in bold show the statistical significance.

TABLE 5 Pooled multivariate hazard ratios and 95% confidence intervals[a] for the association between meat consumption (quantity) and colorectal cancer in women

Meat types	Meat intake, quantity				*P* for trend	Heterogeneity[b] *P*, I^2 (%)	As continuous variable[c]
	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)			
	Colorectal cancer						
Unprocessed red meat	1.00 (Ref.)	1.04 (0.89-1.20)	0.95 (0.76-1.20)	1.06 (0.91-1.24)	.67	1.00, 0.0	1.07 (0.88-1.31)
Beef	1.00 (Ref.)	1.12 (0.97-1.30)	0.94 (0.72-1.23)	1.09 (0.94-1.28)	.58	.77, 0.0	1.35 (0.84-2.18)
Pork	1.00 (Ref.)	1.08 (0.93-1.25)	0.92 (0.74-1.13)	1.04 (0.89-1.22)	.91	.84, 0.0	1.01 (0.79-1.29)
Processed red meat	1.00 (Ref.)	1.04 (0.89-1.21)	1.14 (0.90-1.45)	1.04 (0.89-1.23)	.29	.99, 0.0	0.86 (0.61-1.21)
Chicken	1.00 (Ref.)	1.04 (0.89-1.22)	1.01 (0.87-1.18)	0.97 (0.78-1.22)	.89	.19, 41.7	0.76 (0.36-1.60)
	Colon cancer						
Unprocessed red meat	1.00 (Ref.)	1.09 (0.92-1.29)	0.89 (0.59-1.34)	1.11 (0.93-1.33)	.52	.79, 0.0	1.04 (0.83-1.30)
Beef	1.00 (Ref.)	1.09 (0.78-1.52)	0.94 (0.59-1.52)	**1.20 (1.01-1.44)**	.11	.65, 0.0	**1.60 (1.04-2.46)**
Pork	1.00 (Ref.)	1.13 (0.95-1.34)	0.98 (0.82-1.17)	1.04 (0.86-1.25)	.90	.78, 0.0	0.91 (0.69-1.22)
Processed red meat	1.00 (Ref.)	1.00 (0.76-1.31)	1.14 (0.88-1.48)	1.05 (0.85-1.31)	.31	.27, 17.7	0.82 (0.44-1.51)
Chicken	1.00 (Ref.)	1.03 (0.85-1.25)	0.99 (0.83-1.18)	0.98 (0.81-1.18)	.73	.30, 6.1	0.77 (0.36-1.65)
	Rectal cancer						
Unprocessed red meat	1.00 (Ref.)	0.92 (0.69-1.22)	1.00 (0.75-1.33)	0.98 (0.73-1.32)	.99	.57, 0.0	1.26 (0.86-1.87)
Beef	1.00 (Ref.)	1.10 (0.84-1.45)	0.91 (0.68-1.22)	0.95 (0.71-1.28)	.49	.77, 0.0	1.16 (0.54-2.48)
Pork	1.00 (Ref.)	0.94 (0.71-1.24)	0.79 (0.56-1.11)	1.04 (0.78-1.39)	.92	.99, 0.0	1.39 (0.90-2.14)
Processed red meat	1.00 (Ref.)	1.04 (0.74-1.47)	1.17 (0.88-1.55)	1.06 (0.60-1.89)	.93	.08, 67.1	0.96 (0.36-2.56)
Chicken	1.00 (Ref.)	1.03 (0.78-1.37)	1.05 (0.79-1.40)	0.99 (0.74-1.33)	.99	.50, 0.0	0.70 (0.28-1.75)
	Proximal colon cancer						
Unprocessed red meat	1.00 (Ref.)	1.16 (0.82-1.63)	0.97 (0.76-1.22)	1.03 (0.81-1.32)	.89	.62, 0.0	0.78 (0.39-1.56)
Beef	1.00 (Ref.)	1.07 (0.61-1.86)	0.95 (0.60-1.50)	1.15 (0.81-1.65)	.49	.20, 38.6	0.54 (0.03-11.29)
Pork	1.00 (Ref.)	1.28 (0.86-1.89)	0.93 (0.73-1.19)	0.96 (0.75-1.23)	.36	.35, 0.0	0.71 (0.47-1.05)
Processed red meat	1.00 (Ref.)	0.92 (0.64-1.33)	1.08 (0.72-1.63)	0.98 (0.76-1.26)	.77	.31, 1.5	0.54 (0.18-1.65)
Chicken	1.00 (Ref.)	0.95 (0.76-1.19)	0.94 (0.75-1.19)	0.87 (0.68-1.10)	.27	.87, 0.0	0.65 (0.28-1.49)
	Distal colon cancer						
Unprocessed red meat	1.00 (Ref.)	1.17 (0.87-1.57)	0.95 (0.52-1.72)	1.20 (0.88-1.63)	.39	.55, 0.0	1.09 (0.75-1.60)
Beef	1.00 (Ref.)	1.08 (0.81-1.45)	1.06 (0.68-1.65)	1.12 (0.82-1.51)	.46	.74, 0.0	1.09 (0.33-3.60)
Pork	1.00 (Ref.)	1.05 (0.78-1.41)	0.98 (0.55-1.73)	1.07 (0.74-1.58)	.98	.25, 23.0	1.18 (0.75-1.86)
Processed red meat	1.00 (Ref.)	1.17 (0.87-1.57)	1.23 (0.91-1.67)	1.20 (0.88-1.64)	.24	.71, 0.0	1.18 (0.66-2.11)
Chicken	1.00 (Ref.)	1.02 (0.56-1.87)	1.07 (0.79-1.46)	1.07 (0.64-1.76)	.47	.14, 54.8	1.05 (0.44-2.53)

[a]Adjusted for age (years, continuous), area, history of diabetes (yes or no), body mass index (14 to <18.5, 18.5 to <22, 22 to <25, 25 to <30, or 30 to <40 kg/m^2), smoking status (never smoker, past smoker, or current smoker), alcohol drinking (never/former drinker, occasional drinker of <once/wk, or current drinker of <23 or ≥23 ethanol g/d), nonoccupational physical activity (Japan Public Health Center-based 5-year follow-up study, metabolic equivalent task-hour, quartiles; Takayama Cohort Study, no, 1-2, or ≥2 h/wk), log-transformed energy intake (continuous), calcium (quartiles), and fiber (quartiles).
[b]For the highest category.
[c]Per 100 g of unprocessed red meat, beef, pork, or chicken and 50 g of processed meat.
Ref., reference.
HRs values in bold show the statistical significance.

an increased risk of CRC associated with higher intake of processed red meat (>5 vs ≤1 serving/wk).[20] Nitrate or nitrite in processed meat could be the underlying reason for this association.[47] During the smoking and curing process of meat, nitrite and nitrogen oxides interact with the secondary amines and N-alkyl amides of red meat and enhance the formation of NOCs.[48,49] The NOCs,

including nitrosamines and nitroso-amides, are carcinogenic in laboratory animals.[50]

In our analysis by colon subsite in women, there was a suggestion of increased risk for DCC associated with frequent consumption of processed red meat (pooled HR of 1.30 for "3 times/wk or more" vs "<1 time/wk category"; 95% CI, 0.99-1.71) but not for PCC. This finding is compatible with those of meta-analyses of prospective studies[19,46] and one recent pooled analysis of 2 large prospective studies.[20] We should note that very few women in the present Japanese cohort (2.4%) consumed processed red meat "almost every day" (the level of which was associated with an increased risk of CRC) during the 1990s and that there was no association in the analysis based on quantitative meat intake. This suggests little public health impact of decreasing intake of processed meat in the prevention of CRC in Japanese individuals.

We found no significant association of chicken intake with cancer risk in the colorectum, colon, and rectum either in men or in women, a finding consistent with the previous meta-analyses of prospective studies.[17,51] In an analysis by colon subsite in women, we found a significantly lower risk of PCC, but not DCC, associated with frequent chicken intake ("≥3 times/wk") (Table S2). This could be solely due to chance; however, a prospective study among 148 610 US adults reported chicken intake was inversely associated with the risk of both PCC and DCC.[52] Due to limited and inconsistent data regarding chicken and cancer risk of colon subsites, further studies are needed to clarify the association.

Several mechanisms have been suggested to explain the association between red meat and processed red meat and the risk of CRC. Red and processed meat could increase the risk of CRC by the formation of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons when cooking meat at high temperature or on open flame, which are potent carcinogens.[53] Moreover, HCAs are also in the group 2 category in the IARC classification.[5] These types of meat might also increase the risk of CRC or colon cancer by the fat peroxidation pathway. The major endogenous genotoxic aldehyde product of this pathway is malondialdehyde,[54] which is mutagenic in human cells.[55] Secondary bile acids produced by anaerobic bacteria in the large bowl from primary bile acids, which are essential to the digestion of animal fat, are thought to be colonic irritants and to have hyperproliferative effects.[56] Furthermore, high red meat intake could increase the risk of CRC or colon cancer by enhancing the endogenous formation of NOCs,[57] most of which are known carcinogens.[37] Human experimental studies also reported that the intake of red meat but not white meat significantly increases the fecal levels of NOCs in a dose-dependent manner.[58]

The present study has several strengths. First, we undertook a meta-analysis of data of the major cohort studies in Japan using a validated dietary questionnaire and used identical categories for meat intake across our incorporated studies. Second, each study was controlled for a common set of variables that are known or suggested to be associated with CRC. Finally, with a large number of participants and incident cases of CRC, we were able to examine the effect of meat with reasonable statistical power.

Our study also has limitations that need to be mentioned. First, of 6 cohorts participating in the present pooled analysis, only 2 used a detailed dietary questionnaire that can provide quantitative estimates of meat intake, whereas others assessed the intake frequency of each meat type using a single question. Such a large difference in the dietary questionnaire does not allow us to obtain summary estimates for all cohorts. Together with analyses by sex and subsite of the colorectum, this has led to numerous statistical test results, inflating the chance of significant associations. Therefore, we mainly discussed findings of the preplanned associations (red meat and colon cancer). Second, we used only baseline information on meat intake and did not consider lifetime intake or changes of intake during follow-up. Third, statistical power might not be sufficient in site-specific analyses. Fourth, although each study was adjusted for important factors associated with CRC, we cannot exclude the possibility of residual confounding factors. Fifth, the style of the questions on meat intake differed by each study, which might lead to a misclassification of meat intake. However, the test for heterogeneity across studies was not statistically significant in most analyses. Sixth, the validity of estimated meat intake used in each participating cohort was low to moderate and tended to be lower in men than in women (red meat, r = 0.21-0.43 in men and r = 0.38-0.53 in women). The measurement error of meat intake might result in biased associations towards the null. The null or weaker association between red meat subtype and colon cancer in men of the present study may be partly due to the gender difference of validity of meat intake. Finally, due to a lack of information on cooking methods, we were unable to examine the association of intake of well-done red meat, which could contain higher levels of HCAs, with CRC risk.

In the present pooled analysis using data from large prospective studies in Japanese men and women, who consume much less meat compared to western population, higher beef intake was associated with an increased risk of cancer of the colon (women) and distal colon (men). Frequent pork intake was also associated with DCC in women, but the association with pork intake seems less consistent than that of beef. Frequent intake of processed red meat was associated with an increased risk of CRC and colon cancer in women, but not in men. Further investigation is required to elucidate the mechanisms underlying the differential association by meat subtype, subsite of the colorectum, and sex.

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DISCLOSURE

The authors declare that they have no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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