Original Article

Red meat intake may increase the risk of colon cancer in Japanese, a population with relatively low red meat consumption

Ribeka Takachi PhD[1,2], Yoshitaka Tsubono PhD[1], Keisuke Baba[3], Manami Inoue PhD[1], Shizuka Sasazuki PhD[1], Motoki Iwasaki PhD[1], and Shoichiro Tsugane PhD[1] for the Japan Public Health Center-based Prospective Study Group

[1]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*
[2]*Department of Community Preventive Medicine, Division of Social and Environmental Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[3]*Tohoku University School of Medicine, Miyagi, Japan*

Asian populations have changed from traditional to Westernized diets, with increased red meat intake. They are suggested to be particularly susceptible to the adverse effects of red meat on the development of colorectal cancers, however, few prospective studies of this putative link have been conducted. We examined associations between the consumption of red and processed meat and the risk of subsite-specific colorectal cancer by gender in a large Japanese cohort. During 1995-1998, a validated food frequency questionnaire was administered to 80,658 men and women aged 45-74 years. During 758,116 person-years of follow-up until the end of 2006, 1,145 cases of colorectal cancer were identified. Higher consumption of red meat was significantly associated with a higher risk of colon cancer among women [multivariate hazard ratios (95%CIs) for the highest versus lowest quintiles (HR): 1.48 (1.01, 2.17; trend p=0.03)], as was higher consumption of total meat among men [HR=1.44 (1.06, 1.98; trend p=0.07)]. By site, these positive associations were found for the risk of proximal colon cancer among women and for distal colon cancer among men. No association was found between the consumption of processed meat and risk of either colon or rectal cancer. In conclusion, red meat intake may modestly increase the risk of colon cancer in middle-aged Japanese, although the highest quintile of red meat consumption could be considered moderate by Western standards.

Key Words: meat, colon cancer, rectal cancer, prospective studies, Japan

INTRODUCTION

The linear increase in the incidence and mortality of colon cancer between 1970 and the mid-1990s among Japanese of both sexes occurred in parallel with an increase in the intake of meat, such as beef and pork products.[1-4] Despite this increase, however, intake is still lower in Japanese than Western populations (approx 78, 130, 160, 185, and 200 g per capita per day in Japan, UK, Italy, France, and US, respectively, according to the FAO food supply database, 1995).[3] Given findings that descendents of Japanese migrants to the US have a higher incidence of colorectal cancer than US-born Caucasians,[5,6] individuals of Asian ethnicity may be particularly susceptible to the adverse effects of the Westernized diet, including red meat intake, owing to exposure to other lifestyle risk factors, the modifying influence of genetic biological susceptibility factors, or both.

A recent joint report by the World Cancer Research Fund/American Institute for Cancer Research concluded that the evidence that red and processed meats are a cause of colorectal cancer is convincing.[7] Most prospective studies to date have been conducted in Western countries,[8-10] however, and we are aware of only five in Asian populations, including the Japanese,[11-15] most of which failed to demonstrate a clear positive association between red or processed meat intake and colorectal cancer risk.

Asian populations tend to differ from Western populations in colonic anatomy and pattern of intracolonic bacteria,[16,17] the latter of which relates to the production of secondary bile acids from primary bile acids (which are required to digest animal fat) and of endogenous *N*-nitroso compounds (NOC).[7,18,19] A number of potential differences in the distribution of possible confounders is also likely, with Asians having a higher distribution of smok-

Corresponding Author: Dr Shizuka Sasazuki, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Tel: +81-3-3542-2511 ext. 3378; Fax: +81-3-3547-8578
Email: ssasazuk@ncc.go.jp
Manuscript received 8 December 2010. Initial review completed 9 March 2011. Revision accepted 16 June 2011.

ers (among men) and higher consumption of salt-preserved fish, the major sources of exogenous NOC,[7,20] as well as a lower prevalence of obesity. Moreover, few prospective studies have evaluated the effect of red meat consumption on the risk of subsite-specific colon cancers, separately by gender,[21-23] although risk factors for and biological pathways of proximal and distal colon carcinogenesis have been suggested to differ. In Japan, incidence rates for colorectal cancer have reached those in Western countries (GLOBOCAN 2002). These findings highlight the importance of studies aimed at characterizing the influence of red meat consumption on the risk of colorectal cancer by sub-site in Asian populations.

In this study, we used a validated comprehensive food frequency questionnaire to examine associations between red meat and the risk of colorectal cancer in a population-based prospective cohort study in Japan. Particular focus was placed on the risk of colorectal cancer according to sub-site in relation to red meat intake.

MATERIALS AND METHODS

Study population

The Japan Public Health Center-based Prospective (JPHC) Study was conducted in two cohorts (Cohort I and II), initiated in 1990-1994. The study population was defined as all registered Japanese inhabitants aged 40-69 years in 11 public health center areas, as identified from the population registries maintained by the local municipalities. The study design has been described in detail previously.[24] The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Participants in the present study were subjects in the JPHC study who responded to a self-administered 5-year follow-up questionnaire, which included comprehensive information on food intake and lifestyle factors, in 1995-1999, at age 45-74 years. This follow-up survey was used as the starting point in the present study. One public health center area (Tokyo) was excluded from the present analysis because cancer incidence data were not available.

After exclusion of 11,943 persons who had died, moved out of a study area, or were lost to follow-up before the starting point of the present study (1995-1999), the remaining 121,134 subjects were eligible for participation. Of these, 98,514 subjects responded to the questionnaire survey (46,029 men, 52,485 women; response rate: 81.3%) and were included in the present study.

Follow-up

Subjects were followed from the starting point (time that the FFQ for 5-year follow-up survey was completed) until December 31, 2006. Changes in residence status, including survival, were obtained annually from the residential registry in each area; or for those who had moved out of the study area, through the municipal office in the area to which they had moved. Mortality data for persons in the residential registry are forwarded to the Ministry of Health, Labour and Welfare, and are coded for inclusion in the national Vital Statistics. Residency registration and death registration are required by the Basic Residential Register Law and Family Registry Law, respectively, and the registries are thought to be complete. During the follow-up period in the present study, 7,658 (7.8%) subjects died, 3,970 (4.0%) moved out of the study area, and 318 (0.3%) were lost to follow-up.

The occurrence of cancer was identified by active patient notification from major local hospitals in the study area and from data linkage with population-based cancer registries, with permission from the local governments responsible for the cancer registries. Colorectal cancer cases were coded according to the International Classification of Diseases for Oncology, Third Edition (C18-C20), with colon cancer as C18 (C18.0-C18.5 for proximal colon cancer and C18.6-C18.7 for distal colon cancer) and rectal cancer as C19 and C20.[25] In our cancer registry system, the proportion of cases for which information was available from death certificates only was 2.6% of colorectal cancers. We confirmed 1,435 cases of newly diagnosed colorectal cancer among the 98,514 subjects by December 31, 2006.

Of the 98,514 respondents, we excluded subjects with a history of cancer (n=4,008), those who did not complete the diet component of the questionnaire (n=1,030), and those with extreme self-reported height or weight (≥200 cm, <20 kg; n=2,456). A history of cancer was defined as a diagnosis of cancer before the starting point or a self-report of cancer in the questionnaires. Of the remaining 91,020 subjects, 4,550 who reported extreme total energy intake (lower and upper 2.5 percentiles: 913 and 3,954 kcal/day, respectively), and subjects for whom values for any of the potential confounders were missing (n=5,812) were excluded, leaving 80,658 subjects (38,462 men, 42,196 women) for final analysis, including 1,145 with colorectal cancer (481 colon and 233 rectal cancer cases in men, and 307 colon and 124 rectal cancer cases in women). By sub-site, proximal and distal colon cancer accounted for 200 and 257 cases in men and 179 and 110 in women, respectively.

Food frequency questionnaire (FFQ)

The FFQ asked about the usual consumption of 138 foods and beverages during the previous year in standard portions/units and nine frequency categories.[26] The FFQ enquired about 16 meat items. The red meat items included 3 beef dishes (steak, grilled beef, and stewed beef), 6 pork dishes (stir-fried pork, deep-fried pork, stewed pork in Western style, stewed pork in Japanese style, pork in soup, and pork liver), 4 processed meat products (ham, sausage or Weiner sausage, bacon, and luncheon meat), and chicken liver. Poultry items included two chicken meals (grilled chicken and deep-fried chicken). Standard portion sizes were specified for each food item in three amount choices: small (50% smaller than standard), medium (same as standard) and large (50% larger). The amount of each food consumed (grams/day) was calculated from the responses. Energy and nutrient intake, excluding heme iron, were calculated using the Standardized Tables of Food Composition, 5th revised edition.[27] Heme iron intake was computed using the following proportions of iron for each type of meat: 69% for beef; 39% for pork, ham, bacon, and luncheon meats; 26% for chicken and fish (19 items); and 21% for liver.

The validity of the FFQ for the assessment of meat intake has been confirmed.[28,29] Spearman's correlation coefficients between energy-adjusted meat intake based on the FFQ and those based on 28-day (or 14-day for one public health center area) dietary records among subsamples of men and women were 0.50 and 0.45 for Cohort I and 0.48 and 0.44 for Cohort II, respectively. Correlation coefficients for the reproducibility of the FFQ administered 1 year apart for men and women were 0.52 and 0.52 for Cohort I and 0.52 and 0.41 for Cohort II, respectively.[29,30] Correlation coefficients for the validity of the FFQ for assessment of specific meats for men were as follows: beef; 0.43, pork; 0.42, processed meat; 0.45, chicken; 0.20. For women as compared with men, the validity of the FFQ was comparable (unpublished data, Nanri, et al).

Statistical analysis

Person-years of follow-up were calculated for each subject from the starting point to the date of diagnosis, date of emigration from the study area, date of death, or end of the follow-up period (December 31, 2006), whichever occurred first. Subjects lost to follow-up were censored on the last confirmed date of presence in the study area. A total of 354,987 and 403,129 person-years for men and women, respectively, were accrued for the present analysis.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for energy-adjusted meat consumption categories in quintiles based on the sex-specific distributions for men and women separately, with the lowest consumption category as the reference, using Cox proportional hazards models with adjustment for potential confounding variables according to the SAS PHREG procedure (SAS software, version 9.1, SAS Institute, Inc., Cary, North Carolina). The assumption of proportional hazards was established graphically; no deviation from proportionality was found. Person-years (follow-up time) was used for the underlying time metric in the Cox regressions. A residual model was used for energy adjustment.[31]

We conducted initial analyses by adjusting for age at the starting point (continuous) and study area (10 PHC districts). In the second multivariate model, we further adjusted for body mass index in kg/m^2 (<19, 19-22.9, 23-24.9, 25-26.9, and ≥27), smoking status (never, past, and current), alcohol consumption (none, occasional, 1-149, 150-299, 300-449, and ≥450 g of ethanol/week), physical activity in metabolic equivalent task-hours/day (<30, 30-34.9, 35-39.9, and ≥40), diabetes who either report of medication use for diabetes or a history of diabetes, screening examinations (yes/no) for fecal occult blood test, barium enema, and colonoscopy and quintiles of total energy, calcium, vitamins D and B-6, folate, and dietary fiber. This multivariate model was further adjusted for dried and salted fish intake in quintiles as a potential proxy for the intake of *N*-nitroso compounds.[20,32,33] Subjects for whom values for any of the potential confounders were missing were excluded from the final analysis, because findings did not materially differ when subjects with missing values were retained in the analyses (*n*=86,470) by assigning dummy variables for missing responses. Further, we conducted an additional analysis with the sub-site of colon cancer (proximal and distal) as endpoints. We also assessed linear associations (trend *p*-values) using the median values of meat intake for each quintile in the hazard models.

We additionally performed sub-group analyses according to age (<60 or ≥60 years), smoking status ("never" for nonsmokers or "past" and "current smoker" for ever smokers), body mass index (<25 or ≥25 kg/m^2), alcohol intake (<150 or ≥150 g ethanol/week, for men only), and Cohort (I or II). We sought to confirm whether extremely high meat affects the risk of colorectal cancer compared with very low meat intake. HRs were calculated for meat consumption categories in deciles. Throughout this paper, all *p*-values are two-sided, and statistical significance was determined at the $p<0.05$ level.

RESULTS

Red meat intake for men and women ranged from a median value of 15.4 and 13.6 g/day, respectively, in the lowest quintile to 102 and 93.0 g/day, respectively, in the highest. Subjects with higher red meat consumption were slightly younger.

Table 1 shows age-adjusted values for subject characteristics according to quintile of red meat consumption. For both men and women, subjects with higher red meat consumption were more likely to be overweight, and less likely to be heavy drinkers or participate in fecal occult blood test screening. They were also more likely to consume lower levels of calcium, dietary fiber, as well as dried and salted fish. Higher red meat intake was not associated with the prevalence of ever smoking, history of diabetes, or level of physical activity.

As shown in Table 2, higher consumption of red meat was significantly associated with a higher risk of colon cancer among women. Although a statistically significant association was not found between red meat consumption and colon cancer among men (point estimates of multivariate HRs increased), a significant association was seen for higher consumption of total meat. A significant association was seen between higher consumption of beef and pork and the risk of colon cancer among women. No association between the consumption of processed meat and risk of colon cancer was seen among either men or women. Positive associations of red meat, beef, and pork with the risk of colon cancer were more clearly seen after adjustment for dried and salted fish as a potential confounding factor than without this adjustment among women, but not among men (data not shown). No association was found between total meat, red meat or specific meat consumption and the risk of rectal cancer in either gender (Table 2). These results were not different substantially from those using gender combined quintiles (data not shown).

HRs for colon cancer among men with higher total meat intake were attenuated by further adjustment for heme iron, but were not substantially changed by further adjustment for saturated fatty acid intake, with corresponding multivariate HRs for the highest versus lowest quintile of 1.30 (95% CI: 0.87, 1.93; trend *p*=0.38) and 1.43 (95% CI: 0.95, 2.16; trend *p*=0.19), respectively. HRs for colon cancer among women with higher red meat intake were not substantially changed by further adjustment for heme iron, but were attenuated by further adjustment for saturated fatty acid intake, with corresponding HRs (95% CI) of 1.62 (1.01, 2.61; trend *p*=0.02) and 1.38 (0.84, 2.27; trend *p*=0.18). We further adjusted for

Table 1. Characteristics of subjects according to quintile (Q) of red meat intake for men and women: the JPHC Study, 1995 and 1998 (*n*= 80,658)

	Men						Women					
	Q1	Q2	Q3	Q4	Q5		Q1	Q2	Q3	Q4	Q5	
Median intake (g)	15	31	46	65	102		14	29	43	60	93	
Range	<24.1	≥24.1, <38.8	≥38.8, <54.6	≥54.6, <78.7	≥78.7		<22.0	≥22.0, <35.8	≥35.8, <50.4	≥50.4, <71.8	≥71.8	
No. of subjects	7,692	7,693	7,692	7,693	7,692		8,439	8,439	8,440	8,439	8,439	
Age	58.1	56.8	56.2	56.0	56.0		58.1	56.9	56.3	56.0	56.0	
(SD†)	(7.7)	(7.7)	(7.7)	(7.8)	(7.7)		(7.6)	(7.6)	(7.6)	(7.8)	(7.8)	
Meat intake (g/day, mean§)												
Total meat	20	39	56	77	127		17	36	52	71	115	
Red meat												
Beef	4	9	13	19	31		3	7	10	15	24	
Pork	8	18	26	37	67		8	18	26	36	65	
Processed meat	2	4	6	8	13		2	4	6	8	12	
Chicken	5	8	10	11	14		5	7	9	10	12	
BMI ≥25kg/m^2 (%¶)	25.7	26.6	27.4	29.7	33.0	**	27.4	27.0	26.6	27.8	31.9	**
Past smoker (%¶)	19.0	18.3	19.1	18.6	17.0		0.8	1.2	1.1	1.3	1.2	
Current smoker (%¶)	47.0	48.5	48.3	47.0	45.1	**	5.8	5.6	5.1	5.7	6.4	
Moderate drinker (>0, <300 g alc/w, %¶)	32.6	36.5	39.0	38.8	37.6	**	11.4	12.7	13.3	12.7	10.2	**
Heavy drinker (≥300 g alc/w, %¶)	39.5	35.7	31.1	27.8	19.5	**	1.9	1.4	1.2	0.7	0.4	**
Physical activity (MET-h‡/day, mean§)	32.9	32.8	32.7	32.5	32.1	**	31.8	32.0	32.0	31.8	31.5	**
Screening examination (yes, %¶)												
Fecal occult blood test	29.8	29.9	30.0	28.2	23.7	**	28.5	29.2	29.9	28.4	23.2	**
Barium enema	6.9	7.5	7.2	7.3	7.2		6.3	5.9	6.0	5.9	7.1	
Colonoscopy	8.6	8.4	8.5	7.9	7.0	**	6.8	6.4	6.7	6.3	6.2	
History of diabetes (%¶)	7.6	7.3	7.0	7.2	6.9		3.8	3.6	3.4	3.2	3.7	
Dietary intake (mean§)												
Total energy, kcal/d	2,132	2,146	2,133	2,105	2,048	**	1,893	1,891	1,872	1,863	1,838	**
Calcium, mg/d	554	534	522	505	462	**	656	624	592	557	491	**
Vitamin D, μg/d	10.1	10.1	10.3	10.4	9.8		10.7	10.4	10.5	10.3	9.3	**
Vitamin B_6, mg/d	1.57	1.58	1.59	1.61	1.60	**	1.54	1.53	1.53	1.53	1.50	**
Folate, μg/day	386	391	393	393	379		452	445	435	425	394	**
Dietary fiber, g/d	12.8	12.6	12.4	12.0	11.0	**	16.0	15.1	14.4	13.6	11.9	**
Dried and salted fish, g/d	20.1	19.2	18.8	18.4	15.4	**	21.1	20.2	19.4	18.6	15.0	**
Saturated fatty acid, g/d	12.7	14.4	16.0	17.89	22.28	**	14.5	16.0	17.1	18.4	22.0	**
Heme iron, mg/d	0.31	0.40	0.48	0.58	0.78	**	0.30	0.38	0.45	0.53	0.70	**

† SD, standard deviation; ‡ MET-h, metabolic equivalent task hours.
§ Values are age-adjusted least square means. ¶ Values are age-standardized proportions. ***p*<0.01; Trend tests across categories of red meat consumption were calculated by analysis of covariance for age-adjusted means and the Cochran-Mantel-Haenszel test for age-adjusted proportions.

cholesterol-lowering medications (4% and 7% user for men and women, respectively) or hormone replacement therapy (2.5% current user for women) in the multivariate analysis, but results for colon and rectal cancer did not substantially changed (data not shown).

On further analysis using of colon cancer sub-sites (proximal and distal) as endpoints, as shown in Table 3, higher consumption of total meat, red meat, and beef was marginally associated with a higher risk of distal colon cancer but not with the risk of proximal colon cancer among men. In contrast, higher consumption of red meat and beef was associated with a higher risk of proximal colon cancer but not with the risk of distal colon cancer among women. Higher consumption of processed meat was not associated with either proximal or distal colon cancer for either gender.

Stratified analyses according to age (<60 or ≥60 years) showed a clearer association between red meat intake and the risk of colon cancer among the older age group than the younger group for both men and women. Corresponding HRs (95% CI) for the older and younger age groups were 1.46 (0.95, 2.23; trend *p*=0.07) and 1.05 (0.66, 1.68; trend *p*=0.87), respectively, among men (259 and 222 cases, respectively), and 1.64 (0.95, 2.82; trend *p*=0.06) and 1.34 (0.78, 2.30; trend *p*=0.20), respectively, among women (152 and 155 cases, respectively). Further, significant positive associations were found between the consumption of total or processed meat for men, and beef or pork for women, and the risk of colon cancer among the older age group only (data not shown), although tests of interaction were not statistically significant between age and red meat, or any meat intake for the risk of colon cancer (data not shown). Stratified analyses according to smoking status (never or ever smoker) showed a clearer positive association between processed meat intake and the risk of colon cancer among male nonsmokers (HR: 1.79; 95% CI: 1.04, 3.10; trend *p*=0.02) than male ever-smokers (HR: 1.10; 95% CI: 0.77, 1.58; trend *p*=0.62), although tests of interaction were not statistically significant. The main results [positive association between total meat (among men), and red meat including beef and pork (among women) and the risk of colon cancer; and no association between meats (combined or separated) and the risk of rectal cancer among either gender] did not substantially changed in analyses stratified by body mass index, alcohol intake, or cohort (data not shown). Also, the results did not substantially changed in the analyses that excluded cases diagnosed during the first two years of follow-up (data not shown). When colon cancer was limited to invasive cases (269 cases in men and 186 in women), point estimates of multivariate HRs increased with red meat intake but did not reach statistically significant levels, with multivariate HRs (95%CIs) for the highest versus lowest quintiles of intake of 1.19 (0.78, 1.82; trend *p*=0.37) for men, 1.39 (0.85, 2.28; trend *p*=0.18) for women, and 1.30 (0.94, 1.78; trend *p*=0.08) for the two genders combined.

Finally, in analyses by deciles of meat consumption, higher processed meat intake showed a marginally significant association with the risk of colon cancer for men but not for women, with multivariate HRs for the highest versus lowest decile of 1.37 (95% CI: 0.92, 2.03; trend *p*=0.05) and 1.67 (95% CI: 0.97, 2.88; trend *p*=0.36), respectively.

Table 2. Hazard ratios and 95% confidence intervals for colon and rectal cancer according to quintiles of meat consumptions for men and women: the JPHC Study, 1995 and 1998–2006 (*n*=38,462 and 42,196 for men and women, respectively)

	Men							Women						
		Colon (481 cases)			Rectal (233 cases)				Colon (307 cases)			Rectal (124 cases)		
	Median (g/d)	Cases	HR†	(95%CI‡)	Cases	HR†	(95%CI‡)	Median (g/d)	Cases	HR†	(95%CI‡)	Cases	HR†	(95%CI‡)
Total meat														
Q1	20	98	1.00	(reference)	60	1.00	(reference)	18	63	1.00	(reference)	31	1.00	(reference)
Q2	39	107	1.25	(0.95, 1.65)	43	0.78	(0.53, 1.16)	36	65	1.14	(0.80, 1.62)	19	0.63	(0.35, 1.12)
Q3	56	99	1.27	(0.95, 1.69)	46	0.89	(0.60, 1.32)	52	46	0.82	(0.56, 1.21)	25	0.89	(0.52, 1.53)
Q4	77	82	1.12	(0.83, 1.52)	47	0.94	(0.63, 1.40)	70	67	1.26	(0.88, 1.81)	28	1.02	(0.59, 1.74)
Q5	117	95	1.44	(1.06, 1.98)	37	0.83	(0.52, 1.30)	107	66	1.35	(0.92, 1.98)	21	0.78	(0.41, 1.46)
trend p			0.07			0.64				0.10			0.83	
Red meat														
Q1	15	103	1.00	(reference)	53	1.00	(reference)	14	63	1.00	(reference)	31	1.00	(reference)
Q2	31	103	1.14	(0.87, 1.50)	46	0.96	(0.64, 1.43)	29	67	1.19	(0.84, 1.69)	20	0.67	(0.38, 1.19)
Q3	46	90	1.08	(0.81, 1.44)	48	1.06	(0.71, 1.58)	43	39	0.70	(0.47, 1.06)	30	1.08	(0.65, 1.81)
Q4	65	94	1.19	(0.89, 1.60)	50	1.16	(0.78, 1.74)	60	68	1.30	(0.91, 1.86)	21	0.77	(0.43, 1.37)
Q5	102	91	1.27	(0.93, 1.74)	36	0.93	(0.58, 1.49)	93	70	1.48	(1.01, 2.17)	22	0.81	(0.43, 1.52)
trend p			0.15			0.99				0.03			0.63	
Beef														
Q1	0.2	102	1.00	(reference)	53	1.00	(reference)	0.1	59	1.00	(reference)	27	1.00	(reference)
Q2	6.0	83	0.88	(0.65, 1.18)	46	0.89	(0.60, 1.33)	3.9	67	1.37	(0.96, 1.94)	30	1.27	(0.75, 2.15)
Q3	11	101	1.23	(0.93, 1.63)	38	0.82	(0.54, 1.25)	8.8	61	1.31	(0.91, 1.89)	24	1.06	(0.61, 1.86)
Q4	19	108	1.35	(1.02, 1.78)	46	1.02	(0.68, 1.53)	15	54	1.26	(0.86, 1.84)	20	0.94	(0.52, 1.72)
Q5	34	87	1.15	(0.85, 1.55)	50	1.16	(0.77, 1.74)	28	66	1.62	(1.12, 2.34)	23	1.11	(0.61, 2.02)
trend p			0.10			0.28				0.04			0.95	
Pork														
Q1	6.5	112	1.00	(reference)	54	1.00	(reference)	6.1	65	1.00	(reference)	24	1.00	(reference)
Q2	15	95	0.94	(0.71, 1.24)	54	1.08	(0.74, 1.58)	15	54	0.92	(0.64, 1.32)	28	1.18	(0.68, 2.05)
Q3	24	86	0.89	(0.67, 1.18)	34	0.71	(0.46, 1.10)	24	62	1.04	(0.73, 1.49)	23	0.97	(0.54, 1.73)
Q4	36	96	1.01	(0.77, 1.34)	50	1.08	(0.72, 1.60)	35	48	0.81	(0.55, 1.20)	25	1.06	(0.60, 1.90)
Q5	62	92	1.06	(0.78, 1.42)	41	0.97	(0.63, 1.51)	59	78	1.42	(0.99, 2.04)	24	1.06	(0.57, 1.97)
trend p			0.53			0.97				0.05			0.97	
Processed meat														
Q1	0.2	106	1.00	(reference)	66	1.00	(reference)	0.4	61	1.00	(reference)	27	1.00	(reference)
Q2	1.9	106	1.11	(0.85, 1.46)	49	0.84	(0.58, 1.21)	2.2	69	1.26	(0.89, 1.79)	27	1.09	(0.64, 1.87)
Q3	3.9	81	0.91	(0.68, 1.22)	35	0.64	(0.42, 0.97)	4.3	60	1.10	(0.76, 1.58)	21	0.85	(0.47, 1.52)
Q4	7.3	89	1.05	(0.79, 1.41)	48	0.91	(0.62, 1.33)	7.6	58	1.12	(0.77, 1.62)	27	1.19	(0.68, 2.08)
Q5	16	99	1.27	(0.95, 1.71)	35	0.70	(0.45, 1.09)	15	59	1.19	(0.82, 1.74)	22	0.98	(0.53, 1.79)
trend p			0.10			0.25				0.64			1.00	
Chicken														
Q1	0.5	103	1.00	(reference)	59	1.00	(reference)	0.5	66	1.00	(reference)	21	1.00	(reference)
Q2	4.3	95	0.99	(0.75, 1.31)	47	0.82	(0.55, 1.20)	4.0	55	0.90	(0.62, 1.29)	29	1.35	(0.76, 2.38)
Q3	7.4	106	1.13	(0.86, 1.49)	40	0.72	(0.48, 1.08)	6.8	75	1.26	(0.90, 1.77)	28	1.33	(0.75, 2.37)
Q4	11	88	1.06	(0.79, 1.42)	48	0.90	(0.61, 1.34)	11	50	0.83	(0.57, 1.21)	20	0.97	(0.52, 1.82)
Q5	21	89	1.11	(0.83, 1.49)	39	0.72	(0.47, 1.09)	19	61	1.01	(0.70, 1.46)	26	1.27	(0.69, 2.32)
trend p			0.44			0.22				0.91			0.80	

† HR, hazard ratio; ‡ CI, confidence interval. Hazard ratio was adjusted for age (continuous), Public Health Center area, Body Mass Index in kg/m^2 (<19, 19–22.9, 23–24.9, 25–26.9, and ≥27), smoking status (never, past, and current), alcohol consumption (non, occasional, 1–149, 150–299, 300–449, and ≥450g ethanol/week), physical activity in metabolic equivalent task-hours/day (<30, 30–34.9, 35–39.9, ≥40), medication use for diabetes, history of diabetes, screening examinations (fecal occult blood test; barium enema; colonoscopy), and quintiles of intake of energy, calcium, vitamin D, vitamin B_6, folate, dietary fiber, and dried and salted fish. Linear trends across quintiles of red meat or other meat intake were tested using the derived variable based on median consumption for each quintile as a continuous variable.

Table 3. Hazard ratios and 95% confidence intervals for colon cancer by sub-site according to quintiles of meat consumptions for men and women, the JPHC Study, 1995 and 1998–2006

	Men						Women					
	Proximal colon (200 cases)			Distal colon (257 cases)			Proximal colon (179 cases)			Distal colon (110 cases)		
	Cases	HR†	(95%CI‡)	Cases	HR†	(95%CI‡)	Cases	HR†	(95%CI‡)	Cases	HR†	(95%CI‡)
Total meat												
Q1	42	1.00	(reference)	52	1.00	(reference)	40	1.00	(reference)	18	1.00	(reference)
Q2	47	1.32	(0.87, 2.01)	52	1.14	(0.78, 1.69)	37	1.01	(0.65, 1.59)	25	1.54	(0.84, 2.85)
Q3	37	1.12	(0.71, 1.76)	56	1.36	(0.92, 2.00)	26	0.72	(0.43, 1.18)	17	1.07	(0.55, 2.1)
Q4	41	1.33	(0.85, 2.08)	40	1.03	(0.67, 1.58)	37	1.07	(0.67, 1.71)	28	1.78	(0.96, 3.3)
Q5	33	1.21	(0.73, 2.01)	57	1.65	(1.09, 2.52)	39	1.23	(0.75, 2.01)	22	1.41	(0.71, 2.79)
trend p		0.52			0.04			0.34			0.35	
Red meat												
Q1	47	1.00	(reference)	52	1.00	(reference)	36	1.00	(reference)	22	1.00	(reference)
Q2	43	1.06	(0.70, 1.61)	54	1.19	(0.81, 1.74)	39	1.21	(0.77, 1.91)	24	1.22	(0.68, 2.18)
Q3	36	0.96	(0.61, 1.49)	49	1.17	(0.79, 1.74)	26	0.82	(0.49, 1.37)	12	0.61	(0.30, 1.25)
Q4	40	1.12	(0.72, 1.73)	51	1.29	(0.87, 1.94)	36	1.21	(0.75, 1.96)	29	1.50	(0.84, 2.68)
Q5	34	1.07	(0.66, 1.75)	51	1.42	(0.92, 2.19)	42	1.57	(0.95, 2.58)	23	1.21	(0.63, 2.32)
trend p		0.74			0.12			0.08			0.41	
Beef												
Q1	50	1.00	(reference)	49	1.00	(reference)	28	1.00	(reference)	29	1.00	(reference)
Q2	36	0.78	(0.50, 1.20)	42	0.92	(0.60, 1.39)	42	1.95	(1.20, 3.16)	21	0.82	(0.46, 1.44)
Q3	42	1.06	(0.70, 1.61)	54	1.35	(0.91, 2.01)	39	1.91	(1.17, 3.12)	18	0.73	(0.40, 1.32)
Q4	40	1.06	(0.69, 1.63)	62	1.58	(1.07, 2.34)	26	1.39	(0.81, 2.40)	24	1.05	(0.60, 1.84)
Q5	32	0.89	(0.56, 1.41)	50	1.36	(0.90, 2.06)	44	2.52	(1.53, 4.14)	18	0.78	(0.42, 1.44)
trend p		0.95			0.04			0.01			0.69	
Pork												
Q1	45	1.00	(reference)	62	1.00	(reference)	36	1.00	(reference)	22	1.00	(reference)
Q2	41	1.02	(0.67, 1.56)	50	0.89	(0.61, 1.29)	40	1.23	(0.78, 1.93)	13	0.65	(0.32, 1.29)
Q3	38	1.01	(0.65, 1.57)	45	0.82	(0.55, 1.21)	34	1.03	(0.64, 1.65)	25	1.22	(0.68, 2.19)
Q4	37	0.99	(0.63, 1.55)	50	0.94	(0.64, 1.38)	24	0.72	(0.42, 1.22)	22	1.06	(0.58, 1.96)
Q5	39	1.17	(0.74, 1.87)	50	1.01	(0.68, 1.52)	45	1.42	(0.88, 2.30)	28	1.42	(0.77, 2.61)
trend p		0.52			0.75			0.32			0.11	
Processed meat												
Q1	36	1.00	(reference)	64	1.00	(reference)	31	1.00	(reference)	26	1.00	(reference)
Q2	51	1.60	(1.04, 2.46)	53	0.92	(0.64, 1.33)	42	1.51	(0.95, 2.42)	23	0.98	(0.55, 1.73)
Q3	37	1.20	(0.75, 1.91)	39	0.73	(0.49, 1.10)	37	1.33	(0.82, 2.16)	19	0.79	(0.43, 1.44)
Q4	39	1.31	(0.82, 2.08)	46	0.93	(0.63, 1.38)	38	1.42	(0.87, 2.31)	18	0.77	(0.42, 1.44)
Q5	37	1.38	(0.85, 2.25)	55	1.19	(0.80, 1.77)	31	1.23	(0.73, 2.07)	24	1.03	(0.57, 1.87)
trend p		0.54			0.19			0.87			0.88	
Chicken												
Q1	42	1.00	(reference)	56	1.00	(reference)	40	1.00	(reference)	21	1.00	(reference)
Q2	38	1.00	(0.64, 1.56)	51	0.95	(0.65, 1.40)	32	0.85	(0.53, 1.37)	20	1.03	(0.55, 1.91)
Q3	43	1.12	(0.73, 1.73)	57	1.14	(0.78, 1.65)	43	1.19	(0.76, 1.84)	28	1.47	(0.83, 2.62)
Q4	35	1.04	(0.66, 1.65)	49	1.08	(0.73, 1.60)	28	0.73	(0.45, 1.20)	21	1.10	(0.59, 2.06)
Q5	42	1.34	(0.85, 2.09)	44	0.99	(0.66, 1.48)	36	0.95	(0.59, 1.51)	20	1.01	(0.53, 1.92)
trend p		0.18			0.96			0.70			0.91	

† HR, hazard ratio; ‡ CI, confidence interval. Hazard ratio was adjusted for age (continuous), Public Health Center area, Body Mass Index in kg/m^2 (<19, 19–22.9, 23–24.9, 25–26.9, and ≥27), smoking status (never, past, and current), alcohol consumption (non, occasional, 1–149, 150–299, 300–449, and ≥450g ethanol/week), physical activity in metabolic equivalent task-hours/day (<30, 30–34.9, 35–39.9, ≥40), medication use for diabetes, history of diabetes, screening examinations (fecal occult blood test; barium enema; colonoscopy), and quintiles of intake of energy, calcium, vitamin D, vitamin B-6, folate, dietary fiber, and dried and salted fish. Linear trends across quintiles of red meat or other meat intake were tested using the derived variable based on median consumption for each quintile as a continuous variable.

The lack of association between red meat or processed meat intake and rectal cancer did not change substantially in the decile analyses, with multivariate HRs (95% CI) for the highest versus lowest decile among men and women of 0.83 (0.42, 1.64; trend p=0.80) and 1.33 (0.60, 2.95; trend p=0.83), respectively, for red meat intake, and 0.68 (0.37,1.24; trend p=0.26) and 1.28 (0.55, 2.96; trend p=0.90), respectively, for processed meat intake.

DISCUSSION

In this population-based prospective cohort study in Japan, we observed that higher consumption of red meat, including beef and pork, was associated with an increased risk of colon cancer among women, and that higher total meat consumption was associated with this cancer among men. By site, these positive associations were found for the risk of distal colon cancer among men and proximal colon cancer among women. No association was found between the consumption of red meat and the risk of rectal cancer in either gender, or between processed meat and the risk of either colon or rectal cancer. The highest quintile of red meat consumption in our cohort (120 and 105 g per day for men and women, respectively, based on a corrected median value according to weighed dietary records among sub-samples[28,29]) could be considered moderate by Western standards, at least.[3]

A number of mechanisms to explain the association between red meat or processed meat and colorectal cancer have been proposed. First, secondary bile acids produced by anaerobic bacteria in the large bowel from primary bile acids, which are essential to the digestion of animal fat, are thought to be colonic irritants and to have hyperproliferative effects.[34] Second, red meat is a major source of heme iron, which has high bioavailability, and iron is thought to be carcinogenic as a prooxidant.[7] Third, red meat intake enhances the production of endogenous NOC by gut bacteria, depending on pH and substrate availability.[7,18,19] Fourth, processed meat is also a candidate exogenous source of NOC, which is formed during the curing process.[7] Finally, potentially carcinogenic heterocyclic amines are formed when muscle meats such as beef, pork, or fish are cooked at high temperatures.[7]

These possible mechanisms of the association between red meat and colon cancer might also explain the association between total meat and colon cancer among men. Point estimates of multivariate HRs increased with red meat intake (but did not reach statistically significant levels), for men. Furthermore, red meat intake accounted for 85% of total meat consumption. Thus, observed results of colon cancer in men might not essentially differ from the results in women. In this study, positive associations between meat and colon cancer were clearer for the older than the younger group. These age differences in association may be partly due to changes in bacterial flora, such as the decline in beneficial bifidobacteria numbers or the increase in pH in the elderly gut,[35,36] both of which affect the production of secondary bile acids or endogenous NOC.

A number of potential differences in the impact of dietary intake on the risk of proximal or distal colon cancers have been suggested. Levels of bile acid metabolites are higher in the right than left colon, while those of a marker of exposure to potentially carcinogenic NOC are higher in the distal than proximal colonic DNA of colorectal cancer patients.[8,37] Gender differences in the risk of subsite-specific colon cancers have also been suggested [37-39] due to the higher intracolonic pH or longer bowel transit time in women than in men, which in turn affects the production of secondary bile acid or NOC. In this study, the association between meat and colon cancer were partly explained by saturated fatty acid for women and heme iron for men. On the other hand, larger number of distal colon cancer cases in men, and proximal colon in women, than opposite sub-site of colon cancer cases might possibly clearly reflect the results of total colon cancer among either gender.

To our knowledge, seven studies have independently reported associations between red meat consumption and the risk of proximal or distal colon cancer.[11,21-23,40-42] Results have shown a relatively consistent stronger positive association for the distal colon: five studies showed a stronger association for distal than proximal colon cancer[11,21-23,40] among men[21,22], women[23], or combined[11,40]; one showed a stronger association for proximal colon cancer[41]; and one found no difference for men and women combined.[42] Only a few prospective studies have evaluated the effect of red meat consumption on the risk of subsite-specific colon cancers separately by gender (men[21,22] or women[23]). Our results for the distal colon in men are consistent with one of these previous studies.[21] The observed site-specific differences in risk between genders, however, suggest possible differences in the etiology of proximal and distal colon cancers that are consistent with women's higher incidence of proximal colon tumors and adenomas in the present and Western populations.[43]

The major strength of the present study is its prospective design, which avoids exposure recall bias. Other strengths include the following: study subjects were selected from the general population; response rate to the questionnaire in this general population setting (81%) was high; and the proportion of losses to follow-up (0.3%) was negligible. Further, the number of exclusions due to missing data on red meat consumption, extreme values of energy as a proxy for dietary information, and extreme values for height and weight was not particularly large (8 percent). Although a difference in incidence among subjects with and without missing or extreme information had the potential to influence the results, no such notable difference was seen. Finally, variation among subjects in red meat consumption was sufficiently large, with a 7-fold difference in median intake between the highest (102 and 93 g for men and women, respectively) and lowest quartile groups (15 and 14 g, respectively) (Table 1). This difference was similar to or greater than those in the 7 [21,23,40,44-48] of 11 studies [21,23,40-42,44-49] which found a significant positive association between red meat intake and the risk of colon and/or rectal cancer in Western countries.

Our study has several potential limitations. First, the validity of the FFQ for meat intake was moderate at best (r=0.48-0.50 for men, r=0.44-0.45 for women),[28,29] and was not substantially different by types of meat. It could be suggested that the observed association with the risk of colon cancer might have underestimated the true magnitude of association consequent to misclassification in the FFQ. The potential attenuation might be equivalent by types of meat. However, this bias may have operated in the same direction for subsite-specific cancers between men and women. On this basis, the contrary results for subsite-specific colon cancer between men and women might not be attributable to the validity of the FFQ. Second, we did not note substantial associations for processed meat, and consumption in the highest category (median 16 and 15 g per day for men and women, respectively) was substantially lower than those for studies in Western countries which found a significant positive association with the risk of colon and/or rectal cancer.[22,40,44,46,47,49] Consumption of processed meat in our cohort was likely not large enough to observe a positive association, and the possibility of an adverse effect on the colon cancer from a greater intake than in our highest quartiles of processed meat cannot be excluded. The different results between pork and processed meat might be partly attributable to relatively low level of processed meat intake among the Japanese. In this study, the results did not support a hypothesis that higher processed meat or other meat intake increases the risk of rectal cancer with these levels. Third, although we measured and adjusted for possible confounding variables to the extent possible, the possibility of confounding by unmeasured variables cannot be totally disregarded. Also, it is possible that some of the significant findings may be due to chance.

In conclusion, in this large-scale, population-based prospective cohort study among middle-aged Japanese men and women, whose consumption of red meat was considered moderate by Western standards, we found that higher consumption of red meat was associated with an increased risk of colon cancer among women, as was higher consumption of total meat among men. The positive associations for subsite-specific colon cancers appeared to differ by gender. The Japanese may be particularly susceptible to the adverse effects of red meat intake in the development of colon cancers.

AUTHOR DISCLOSURES

This research was supported by Grants in Aid for Cancer Research and for the Third-Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan. The funding agencies had no role in the research presented herein, and the researchers were fully independent in pursuing this research. None of the authors declares a personal or financial conflict of interest.

REFERENCES

1. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare: Vital Statistics of Japan 2000, Tokyo: Health and Welfare Statistics Association; 2002.
2. Cancer incidence and incidence rates in Japan in 1998: estimates based on data from 12 population-based cancer registries. Jpn J Clin Oncol. 2003;33:241-5.
3. FAO (2007) FAOSTAT: Production, ProSTAT, Crops: Food and Agriculture Organization of the United Nations. [cited 2010/9/27]; Available from: http://faostat.fao.org/
4. Ministry of Health, Labour and Welfare/ Society for the information on Health and Nutrition. The National Health and Nutrition Survey in Japan, 2005. Tokyo: Daiichi Publishing; 2008.
5. Flood DM, Weiss NS, Cook LS, Emerson JC, Schwartz SM, Potter JD. Colorectal cancer incidence in Asian migrants to the United States and their descendants. Cancer Causes Control. 2000;11:403-11.
6. Marchand LL. Combined influence of genetic and dietary factors on colorectal cancer incidence in Japanese Americans. J Natl Cancer Inst Monogr. 1999;(26):101-5.
7. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, physical activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research; 2007.
8. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer. 2006;119:2657-64.
9. Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. Int J Cancer. 2002;98:241-56.
10. Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. Cancer Epidemiol Biomarkers Prev. 2001;10:439-46.
11. Sato Y, Nakaya N, Kuriyama S, Nishino Y, Tsubono Y, Tsuji I. Meat consumption and risk of colorectal cancer in Japan: the Miyagi Cohort Study. Eur J Cancer Prev. 2006; 15:211-8.
12. Kojima M, Wakai K, Tamakoshi K, Tokudome S, Toyoshima H, Watanabe Y et al. Diet and colorectal cancer mortality: results from the Japan Collaborative Cohort Study. Nutr Cancer. 2004;50:23-32.
13. Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. Cancer Lett. 2006;244:260-7.
14. Lee SA, Shu XO, Yang G, Li H, Gao YT, Zheng W. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. Nutr Cancer. 2009;61: 194-205.
15. Khan MM, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T, Sakauchi F, Washio M, Mori M. Dietary habits and cancer mortality among middle aged and older Japanese living in hokkaido, Japan by cancer site and sex. Asian Pac J Cancer Prev. 2004;5:58-65.
16. Benno Y, Suzuki K, Suzuki K, Narisawa K, Bruce WR, Mitsuoka T. Comparison of the fecal microflora in rural Japanese and urban Canadians. Microbiol Immunol. 1986; 30:521-32.
17. Saunders BP, Masaki T, Sawada T, Halligan S, Phillips RK, Muto T, Williams CB. A peroperative comparison of Western and Oriental colonic anatomy and mesenteric attachments. Int J Colorectal Dis. 1995;10:216-21.
18. Bingham SA. High-meat diets and cancer risk. Proc Nutr Soc. 1999;58:243-8.
19. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. Environ Mol Mutagen. 2004;44:44-55.
20. Dich J, Jarvinen R, Knekt P, Penttila PL. Dietary intakes of nitrate, nitrite and NDMA in the Finnish Mobile Clinic Health Examination Survey. Food Addit Contam. 1996; 13:541-52.
21. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res. 1994;54: 2390-7.
22. Wu K, Giovannucci E, Byrne C, Platz EA, Fuchs C, Willett WC, Sinha R. Meat mutagens and risk of distal colon adenoma in a cohort of U.S. men. Cancer Epidemiol Biomarkers Prev. 2006;15:1120-5.
23. Larsson SC, Rafter J, Holmberg L, Bergkvist L, Wolk A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. Int J Cancer. 2005;113:829-34.
24. Tsugane S, Sobue T. Baseline survey of JPHC study--design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol. 2001;11:S24-9.
25. World, Health, and Organization. International Classification of Diseases for Oncology, 3rd ed. Geneva, Switzerland: World Health Organization;2000.
26. Tsubono Y, Takamori S, Kobayashi M, Takahashi T, Iwase Y, Iitoi Y, Akabane M, Yamaguchi M, Tsugane S. A data-

based approach for designing a semiquantitative food frequency questionnaire for a population-based prospective study in Japan. J Epidemiol. 1996;6:45-53.
27. Resource Council. Science and Technology Agency. The Govenrment of Japan. Standard Tables of Food Composition in Japan, the fifth revised edition. Tokyo: Printing Bureau, Ministry of Finance; 2002.
28. Sasaki S, Kobayashi M, Tsugane S. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for food groups. J Epidemiol. 2003;13:S57-63.
29. Ishihara J, Sobue T, Yamamoto S, Yoshimi I, Sasaki S, Kobayashi M et al. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J Epidemiol. 2003;13:S134-47.
30. Sasaki S, Ishihara J, Tsugane S. Reproducibility of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess food and nutrient intake. J Epidemiol. 2003;13:S115-24.
31. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998.
32. Knekt P, Jarvinen R, Dich J, Hakulinen T. Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. Int J Cancer. 1999;80:852-6.
33. Takachi R, Inoue M, Shimazu T, Sasazuki S, Ishihara J, Sawada N et al. Consumption of sodium and salted foods in relation to cancer and cardiovascular disease: the Japan Public Health Center-based Prospective Study. Am J Clin Nutr. 2010;91:456-64.
34. Nagengast FM, Grubben MJ, van Munster IP. Role of bile acids in colorectal carcinogenesis. Eur J Cancer. 1995;31A: 1067-70.
35. Enck P, Zimmermann K, Rusch K, Schwiertz A, Klosterhalfen S, Frick JS. The effects of ageing on the colonic bacterial microflora in adults. Z Gastroenterol. 2009;47:653-8.
36. Woodmansey EJ. Intestinal bacteria and ageing. J Appl Microbiol. 2007;102:1178-86.
37. Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer. 2002;101:403-8.
38. McMichael AJ, Potter JD. Diet and colon cancer: integration of the descriptive, analytic, and metabolic epidemiology. Natl Cancer Inst Monogr. 1985;69:223-8.
39. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. J Natl Cancer Inst. 1985; 75:185-91.
40. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst. 2005;97:906-16.
41. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, Rodriguez C, Sinha R, Calle EE. Meat consumption and risk of colorectal cancer. JAMA. 2005;293: 172-82.
42. Rohrmann S, Hermann S, Linseisen J. Heterocyclic aromatic amine intake increases colorectal adenoma risk: findings from a prospective European cohort study. Am J Clin Nutr. 2009;89:1418-24.
43. McCashland TM, Brand R, Lyden E, de Garmo P. Gender differences in colorectal polyps and tumors. Am J Gastroenterol. 2001;96:882-6.
44. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med. 1990;323:1664-72.
45. Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. Cancer Causes Control. 2002;13:383-93.
46. English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, Giles GG. Red meat, chicken, and fish consumption and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2004;13:1509-14.
47. Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med. 2007;4:e325.
48. Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. Br J Cancer. 2007;97:118-22.
49. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk factors for colon and rectal cancer. Int J Cancer. 2004;108:433-42.

Original Article

Red meat intake may increase the risk of colon cancer in Japanese, a population with relatively low red meat consumption

Ribeka Takachi PhD[1,2], Yoshitaka Tsubono PhD[1], Keisuke Baba[3], Manami Inoue PhD[1], Shizuka Sasazuki PhD[1], Motoki Iwasaki PhD[1], and Shoichiro Tsugane PhD[1] for the Japan Public Health Center-based Prospective Study Group

[1]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*
[2]*Department of Community Preventive Medicine, Division of Social and Environmental Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[3]*Tohoku University School of Medicine, Miyagi, Japan*

在一個紅肉攝取相對較低民族日本，攝取較多紅肉會增加結腸癌罹患風險

亞洲人口飲食從傳統飲食轉變為西式飲食，紅肉的攝取量也隨之增加。然而，一些前瞻性研究已證實，這些人的結腸直腸癌的發展最可能受到攝取紅肉的不良影響。我們在一個日本的大型世代研究，評估男女性在紅肉及加工肉品的攝取與特定部位結腸直腸癌的罹患風險之間的相關性。在 1995-1998 年間，80,658 位 45-74 歲男女性填寫了一份經過效度測試食物頻率問卷。至 2006 年底，共追蹤了 758,116 人年，有 1,145 個結腸直腸癌病例被診斷。紅肉攝取較高的女性參與者，其罹患結腸癌的風險顯著較高[攝取最多的五分之一比起最低的五分之一，其複迴歸危害比(95%信賴區間)：1.48 (1.01, 2.17; 趨勢 *p*=0.03)]；男性則是總肉類攝取較高者，其風險也顯著較高[危害比=1.44 (1.06, 1.98; 趨勢 *p*=0.07)]。就特定部位而言，女性在近端結腸癌具有正相關，而男性則為遠端結腸。加工肉品的攝取與罹患結腸或直腸癌的風險皆不具相關性。總之，以西方的標準而言，中年日本人攝取紅肉最多的五分之一的量僅算中等量，但是已經足以增加罹患風險。

關鍵字:肉、結腸癌、直腸癌、前瞻性研究、日本