RESEARCH COMMUNICATION

The Risk of Colorectal Cancer is Associated with the Frequency of Meat Consumption in a Population-based Cohort in Korea

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Abstract

Objective: To date, there have been few prospective cohort studies that have investigated the association between meat consumption and the risk of colorectal cancer (CRC) in Asian countries. A large, population-based cohort study was conducted to assess the effect of the frequency of meat consumption on the risk of CRC in Korean adults. Methods: The participants were Korean government employees, school faculty members, and their unemployed dependents, aged 30–80 years, who underwent health examinations between 1996 and 1997. In 2003, information on CRC incidence was obtained during the 6–7 year follow-up period. The final data analysis included 2,248,129 study subjects. The hazard ratio (HR) and 95% confidence interval (CI) of the HR were estimated using the Cox proportional hazards regression model. Results: During the follow-up period, CRC occurred in 4,501 men and 1,943 women (64.19 and 36.34 for age-standardized incidence rates per 100,000 person-years, respectively). In the total population, the estimated HRs and 95% CI for meat consumption of 2–3 times per week and more than 4 times per week compared with consumption of less than once per week were 1.06 (1.01–1.12) and 1.23 (1.13–1.35), respectively. In men only and women only groups, the HRs (95% CI) for consumption of more than 4 times per week compared with consumption of less than once per week were 1.13 (1.02–1.26) and 1.42 (1.21–1.66), respectively. Conclusion: The present findings suggest that frequency of meat consumption is positively associated with the risk of CRC.

Key words: meat - colorectal cancer - prospective study - cohort

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Introduction

In most of the industrialized world, colorectal cancer (CRC) ranks among the most prevalent and lethal types of cancer (Parkin et al., 2005). Recently, the incidence rate of CRC in Korea has increased markedly in both men and women (Jung et al., 2009). Between 1999 and 2008, the incidence rate for CRC increased from 27.0 to 47.0 per 100,000 person-years among men and from 17.1 to 25.6 per 100,000 person-years among women. This trend may be related to the adoption of a more westernized lifestyle, including dietary habits such as increases in both the frequency and amount of meat consumed (Kim et al., 2009). According to the 2nd report of the World Cancer Research Fund/American Institute of Cancer Research, the evidence that red meats and processed meats are a cause of CRC seems at least more than probable. However, most of the studies on this subject have been conducted in Western countries and, to date, there have been few studies that have investigated the association between meat consumption and colorectal carcinogenesis in Asian countries. In the present investigation, we conducted a large, population-based, cohort study to assess the effect of the frequency of meat consumption on the risk of CRC in Korean adults.

Materials and Methods

Study population

The participants were Korean government employees, school faculty members, and their unemployed dependents, aged 30–80 years, who underwent a health examination between 1996 and 1997.

The examination was conducted by the Korean Health Insurance Corporation, a major institution that provides a nationwide health insurance system in Korea. This study analyzed data obtained during regular medical check-ups and from the Korean Central Cancer Registry. Because the study involved routinely collected medical data, participant consent was not required. Incident cancer cases were identified from the cancer registry, and the collected data included the time of diagnosis and the type

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of cancer. The study was approved by the institutional review board of the National Cancer Center (IRB No. NCCNCS09-305) and the need for consent was waived by the ethics committee.

Of the 5,657,474 individuals, those who provided incomplete information on their cancer history, dietary habits, body mass index (BMI), alcohol consumption and smoking habits, physical activity, and family cancer history were excluded. Those who had previously had any cancer (13,622 men and 7,067 women) were also excluded from the data analysis. A total of 2,248,129 study subjects were included in the final data analysis.

Information on health-related behavior was collected using a self-administered questionnaire during the health examination. Questions on dietary habits, the main variable of interest, pertained to the following: salt preference (not salty, medium, salty), diet preference (vegetables preferred, both animal products and vegetables, animal products preferred), and frequency of meat consumption (≤1 time per week, 2–3 times per week, ≥4 times per week). Other questions on health-related behaviors included those on personal cancer history, family cancer history, alcohol intake [none, light (<51.8 g per week), medium (51.8–124.1 g per week), and heavy (>124.1 g per week)], smoking (never, ex-smoker, less than half a pack per day, between half and 1 pack per day, and more than one pack per day), and physical activity [none, low (active >5 times per week, <30 min each time), moderate (active >5 times per week, <30 min each time or active >2 times per week, >30 min each time), heavy (active >5 times per week, >30 min each time)]. Weight and height were also measured during the health examination. BMI was calculated as the weight in kilograms divided by the height in meters squared. Participants were categorized into 4 groups on the basis of their BMI: <18.5, 18.5–23.0, >23.0–25.0, and >25.0 kg/m2.

Cancer incidence

We identified study subjects who were diagnosed with cancer up to 2003 through data linkage with the Korea National Cancer Incidence Database (KNCIDB) of the Korea Central Cancer Registry (Shin et al., 2005). Codes C00–C99 in the International Classification of Diseases (10th Edition) were used to identify the cancers, and codes C18–C20 were used for CRC (WHO).

Statistical analyses

Age-standardized incidence rates were calculated by weighting the rate of a standardized population from each age group using the WHO world standard population: age-standardized incidence rate = [Σ [(crude incidence rate for each age group) × (world standard population size for each age group)/total world standard population size] (Segi). A Mantel-Haenszel chi-square test was used to compare strata in terms of age, BMI, alcohol intake, smoking habits, physical activity, and family history of cancer. The hazard ratio (HR) and 95% confidence interval (CI) of the HR were estimated using the Cox proportional hazards regression model. The proportionality assumption of the model was tested and adjustments were made for age, sex, BMI, smoking habits, alcohol consumption, physical activity, and family history of cancer in the multivariate analyses. All the analyses were performed using the SAS statistical package (9.1.3; SAS Institute, Cary, NC), and a P value of <0.05 was considered significant.

Results

The data from 2,248,129 study subjects (1,420,981 men and 827,148 women) were analyzed to assess the association between dietary habits and CRC risk. Table 1 shows the distribution of general characteristics. During the 7-year follow-up, CRC occurred in 4,501 men and 1,943 women. In the total population, there were statistically significant differences in the distribution of age, BMI, alcohol intake, smoking, and physical activity between those who had CRC and those who did not have CRC. In men, the factors that were found to be significant were age, BMI, alcohol intake, smoking, and physical activity, whereas in women, age, BMI, and smoking habits were statistically significant factors. In the total population, and the men only and women only groups, those with CRC tended to be older, had a BMI >25 kg/m2, and were less likely to have a history of smoking compared with subjects without CRC. In addition, those without CRC had a lower alcohol intake than colorectal patients in the total population and men only group.

Table 2 lists the age-standardized incidence rates per 100,000 person-years for the total population (51.17), men only (64.19), and women only (36.34). An association was found between CRC risk and dietary habits. There was a significant evidence of an increased risk of CRC with the frequency of meat consumption. In the total population, the estimated HRs and 95% CI for consumption of meat 2–3 times per week and of more than 4 times per week compared with consumption of less than once per week were 1.06 (1.01–1.12) and 1.23 (1.13–1.35), respectively. In the men only and women only groups, the HRs (95% CI) for a meat consumption of more than 4 times per week compared with a consumption of less than once per week were 1.13 (1.02–1.26) and 1.42 (1.21–1.66), respectively. Associations with other variables related to dietary habits, such as salt preference, and meal preference, were not statistically significant.

Discussion

In the present large population-based cohort study, we confirmed that the frequency of meat consumption was significantly associated with a risk of CRC in Korean adults. We were also able to compare the age-standardized incidence rate for CRC with that of nationwide data from the Korean Central Cancer Registry and to confirm similar figures between the two (51.17,

Table 1. General Characteristics of the Study Participants

Category		Total (N=2,248,129) Without CRC (%) (N=2,241,685)	Total With CRC (%) (N=6,444)	P†	Men (N=1,420,981) Without CRC (%) (N=1,416,480)	Men With CRC (%) (N=4,501)	P†	Women (N=827,148) Without CRC (%) (N=825,205)	Women With CRC (%) (N=1,943)	P†
Age group										
	30-39 years	648,592 (28.9)	424 (6.6)	<0.0001	499,067 (35.2)	344 (7.6)	<0.0001	149,525 (18.1)	80 (4.1)	<0.0001
	40-49 years	776,272 (34.6)	1,423 (22.1)		462,721 (32.7)	990 (22.0)		313,551 (38.0)	433 (22.3)	
	50-59 years	507,808 (22.7)	2,243 (34.8)		301,996 (21.3)	1,650 (36.7)		205,812 (24.9)	593 (30.5)	
	60-69 years	240,163 (10.7)	1,702 (26.4)		121,722 (8.6)	1,128 (25.1)		118,441 (14.4)	574 (29.5)	
	70-80 years	68,850 (3.1)	652 (10.1)		30,974 (2.2)	389 (8.6)		37,876 (4.6)	263 (13.5)	
BMI										
	< 18.5 kg/m2	67,387 (3.0)	186 (2.9)	<0.0001	34,423 (2.4)	122 (2.7)	<0.0001	32,964 (4.0)	64 (3.3)	<0.0001
	18.5 - 23.0 kg/m2	937,758 (41.9)	2,396 (37.2)		579,872 (41.0)	1,686 (37.5)		357,886 (43.4)	710 (36.6)	
	23.0 - 25.0 kg/m2	602,879 (26.9)	1,814 (28.2)		401,810 (28.4)	1,318 (29.3)		201,069 (24.4)	496 (25.5)	
	≥ 25.0 kg/m2	631,905 (28.2)	2,046 (31.8)		399,454 (28.2)	1,374 (30.5)		232,451 (28.2)	672 (34.6)	
Alcohol Intake§										
	None	542,727 (37.5)	1,586 (39.2)	0.0002	149,100 (15.8)	648 (22.5)	<0.0001	393,627 (78.2)	938 (80.1)	0.1117
	Light	760,859 (52.6)	2,149 (53.1)		652,085 (69.1)	1,918 (66.7)		108,774 (21.6)	231 (19.7)	
	Moderate	85,358 (5.9)	170 (4.2)		84,598 (9.0)	169 (5.9)		760 (0.2)	1 (0.1)	
	Heavy	57,912 (4.0)	143 (3.5)		57,538 (6.1)	142 (4.9)		374 (0.1)	1 (0.1)	
Smoking Amount										
	Never	921,074 (48.0)	2,550 (45.4)	0.0116	381,710 (28.4)	1,313 (30.9)	<0.0001	539,364 (94.2)	1,237 (90.8)	<0.0001
	Ex-smoker	207,734 (10.8)	886 (15.8)		200,141 (14.9)	857 (20.2)		7,593 (1.3)	29 (2.1)	
	< 1/2 pack currently	145,045 (7.6)	494 (8.8)		130,062 (9.7)	436 (10.3)		14,983 (2.6)	58 (4.3)	
	1/2 – 1 pack currently	465,761 (24.3)	1,256 (22.4)		456,952 (33.9)	1,224 (28.8)		8,809 (1.5)	32 (2.4)	
	> 1 pack currently	179,632 (9.4)	431 (7.7)		177,590 (13.2)	424 (10.0)		2,042 (0.4)	7 (0.5)	
Physical Activity¶										
	None	1,214,457 (57.2)	3,309 (54.3)	<0.0001	657,987 (47.9)	2,009 (46.6)	0.0191	556,470 (74.1)	1,300 (73.1)	0.6307
	Low	272,812 (12.8)	844 (13.9)		219,781 (16.0)	697 (16.2)		53,031 (7.1)	147 (8.3)	
	Moderate	506,360 (23.8)	1,497 (24.6)		403,821 (29.4)	1,263 (29.3)		102,539 (13.7)	234 (13.2)	
	Heavy	131,076 (6.2)	439 (7.2)		92,171 (6.7)	342 (7.9)		38,905 (5.2)	97 (5.5)	
Family History of Cancer	No	1,137,670 (81.0)	3,305 (80.8)	0.7952	722,940 (81.7)	2,318 (81.5)	0.7797	414,730 (79.7)	987 (79.2)	0.6562
	Yes	267,443 (19.0)	785 (19.2)		161,535 (18.3)	525 (18.5)		105,908 (20.3)	260 (20.9)	

†Age-standardized Incidence Rate (AIR) = Σ [(crude incidence rate for each age group) X (world standard population size for each age group) / total world standard population size]; §The hazard ratio (HR) and 95% confidence interval (CI) of the HR were estimated using the Cox proportional hazards regression model. The proportionality assumption of the model was tested and adjustments were made for age, sex, BMI, smoking habits, alcohol consumption, physical activity, and family history of cancer

Table 2. Association between the Risk of Colorectal Cancer and Dietary Habits

		Without CRC	With CRC	AIR†	Crude HR (95%CI)	Multivariate HR§ (95%CI)
Total (N=2,248,129)						
Salt preference	Not salty	1,446,898	4,043		1.00 (referent)	1.00 (referent)
	Medium	356,997	1,057		0.94 (0.88-1.01)	1.00 (0.93-1.07)
	Salty	437,790	1,344		1.04 (0.96-1.13)	1.04 (0.96-1.13)
Meal preference	Mostly vegetables	569,972	1,689		1.00 (referent)	1.00 (referent)
	Animal products and vegetables	1,515,743	4,286		0.94 (0.89-0.99)	0.98 (0.93-1.04)
	Animal products preferred	155,970	469		1.00 (0.90-1.10)	1.03 (0.92-1.14)
Meat frequency	≤ once/week	1,115,368	3,083		1.00 (referent)	1.00 (referent)
	2–3 times/week	993,904	2,817		1.03 (0.97-1.08)	1.06 (1.01-1.12)
	≥ 4 times/week	32,413	544		1.58 (1.44-1.73)	1.23 (1.13-1.35)
Total		2,241,685	6,444	51.17		
Men (N=1,420,981)						
Salt preference	Not salty	888,012	2,813		1.00 (referent)	1.00 (referent)
	Medium	226,689	733		0.98 (0.90-1.06)	1.01 (0.93-1.09)
	Salty	301,779	955		0.99 (0.87-1.09)	1.00 (0.91-1.11)
Meal preference	Mostly vegetables	288,458	945		1.00 (referent)	1.00 (referent)
	Animal products and vegetables	1,008,859	3,175		0.96 (0.89-1.03)	0.98 (0.91-1.05)
	Animal products preferred	119,163	381		0.98 (0.87-1.11)	1.00 (0.89-1.13)
Meat frequency	≤ once/week	652,307	2,025		1.00 (referent)	1.00 (referent)
	2–3 times/week	688,672	2,123		0.99 (0.93-1.05)	1.05 (0.99-1.12)
	≥ 4 times/week	75,501	353		1.57 (1.41-1.76)	1.13 (1.02-1.26)
Total		1,416,480	4,501	64.19		
Women (N=827,148)						
Salt preference	Not salty	558,886	1,230		1.00 (referent)	1.00 (referent)
	Medium	130,308	324		0.88 (0.78-1.00)	0.95 (0.84-1.08)
	Salty	136,011	389		1.16 (1.00-1.34)	1.13 (0.97-1.31)
Meal preference	Mostly vegetables	281,514	744		1.00 (referent)	1.00 (referent)
	Animal products and vegetables	506,884	1,111		0.82 (0.75-0.90)	0.96 (0.88-1.06)
	Animal products preferred	36,807	88		0.89 (0.71-1.11)	1.06 (0.85-1.33)
Meat frequency	≤ once/week	463,061	1,058		1.00 (referent)	1.00 (referent)
	2–3 times/week	305,232	694		1.02 (0.92-1.12)	1.07 (0.97-1.18)
	≥ 4 times/week	56,912	191		1.57 (1.34-1.83)	1.42 (1.21-1.66)
Total		825,205	1,943	36.34		

†Age-standardized Incidence Rate (AIR) = Σ [(crude incidence rate for each age group) X (world standard population size for each age group) / total world standard population size]; §The hazard ratio (HR) and 95% confidence interval (CI) of the HR were estimated using the Cox proportional hazards regression model. The proportionality assumption of the model was tested and adjustments were made for age, sex, BMI, smoking habits, alcohol consumption, physical activity, and family history of cancer

64.19, and 36.34 per 100,000 person-years for the total population, men only, and women only in this study vs. 47.60, 61.23, and 37.03 per 100,000 person-years, respectively, in the nationwide data).

The 2nd report of the World Cancer Research Fund/ American Institute of Cancer Research summarized the findings of previous similar studies (16 cohort studies and 71 case-control studies) that investigated the association between red meat consumption and CRC. All except one of the cohort studies that analyzed the risk for the highest intake group versus the lowest reported increased risk, which was statistically significant. Meta-analysis was possible on 7 studies that measured red meat intake in terms of "times per week" and on 3 studies that measured intake in terms of grams per day. The summary effect estimates were 1.43 (95% CI 1.05–1.94) per times/day and 1.29 (95% CI 0.94–1.78) per 100 g/day, respectively. These data are supported by a recently published meta-analysis (Larsson and Wolk, 2006) of 15 prospective studies, which reported a summary effect estimate of 1.28 (95% CI 1.18–1.39) per 120 g red meat/day.

A potential mechanism to explain the possible association between meat intake and colorectal cancer concerns the various chemicals found in meat and meat products. These include heme iron, nitrates, and heterocyclic amines (Cross et al., 2010). Iron can induce oxidative DNA damage (Glei et al., 2002, Tappel, 2007) and heme iron has been postulated to be associated with fecal water cytotoxicity (Sesink et al., 1999, Sesink et al., 2000). Furthermore, heme iron intake increases endogenous formation of N-nitroso compounds (Cross et al., 2003), which are multisite carcinogens (Lijinsky). Meat cooked well-done at high temperature is also a source of heterocyclic amines (Sinha et al., 1998a, Sinha et al., 1995, Sinha et al., 1998b) and polycyclic aromatic hydrocarbons (Culp et al., 1998, Kazerouni et al., 2001), which are known gastrointestinal carcinogens in animal models (Culp et al., 1998, Ohgaki et al., 1991).

Despite such a strong judgment, in an early ecological study, no significant correlation was observed between beef consumption and age-adjusted colorectal cancer incidence and mortality rates (Enstrom, 1975). Findings from human studies have been relatively inconsistent. Furthermore, there is no clear evidence of dose-response and patterns of association vary by study characteristics. Trustwell also suggested that the evidence supporting the level up to 'convincing' was not accurate and nor complete due to omissions and errors in the 2nd report of the World Cancer Research Fund/American Institute of Cancer Research (Truswell, 2009). The most recent literature has critically summarized prospective epidemiologic studies: it is not sufficient to support an independent positive association on red meat and colorectal cancer (Alexander and Cushing, 2010). An updated meta-analysis on prospective studies of red meat consumption and colorectal cancer reported an equivocal conclusion between red meat intake and colorectal cancer due to many unanswered scientific questions (e.g., an exposure not specific to meat intake, other dietary sources such as vegetables or cereal products, and confounding lifestyle patterns (Alexander et al., 2011). Therefore, further evaluation of association may help in elucidating the relationship between red meat consumption and colorectal cancer.

This study has several strengths. Most notable among these is the use of a population-based cohort study design with follow-up of a large number of subjects and medically confirmed diagnoses of cancer. This enabled us to minimize the recall/selection bias, and thereby reduce the potential for misclassification. To the best of our knowledge, this is the first study of diet and CRC risk to explore the association in a large sample of Koreans using a population-based, cohort study design.

However, one of the limitations of this study is the lack of detailed information on the amount of meat that was regularly consumed. That is, we were not able to determine the absolute amount of meat consumed. The only information obtained using the questionnaire survey was related the frequency of weekly meat consumption, and then only with 3 categories: less than once, 2–3 times, and more than 4 times. In addition, we were unable to classify meat consumption into different components, such as red meat, white meat, and processed meat. Previous studies have reported different results depending on various components of meats (Cross et al., 2010) since different meats contain varying amounts of heme iron, nitrate, and heterocyclic amines. Furthermore, in the present study, we obtained no information on the cooking methods used. Meat is a source of potentially carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons, which are formed in meats cooked at high temperature (Ohgaki et al., 1991, Sinha et al., 1998a, Sinha et al., 1995, Sinha et al., 1998b). A further limitation is that we were unable to control for other potential confounders such as income and occupation. The only confounding factors taken into consideration were age, smoking, alcohol consumption, physical activity, and a family history of cancer.

Further studies should include information on a wide range of meat intake and the administration of a detailed meat questionnaire enabling the investigation of multiple components such as meat type (red meat, white meat, processed meat) and cooking method (roasting, grilling, broiling, charcoaling, deep-frying, canning). Moreover, future studies should focus on differential risks at different anatomical subsites, such as the colon or rectum, left side or right side, distal or proximal, etc., since some studies have shown differences in incidence according to subsite (Chao et al., 2005, Hu et al., 2007, Iacopetta, 2002, Larsson et al., 2005, Norat et al., 2005, Povey et al., 2000). For example, risks have been shown to be higher for rectal cancer than for colon cancer (Cross et al., 2010). However, controversy remains as to whether the association between dietary factors and rectal cancer is as strong as that between dietary factors and colon cancer (Pietinen et al., 1999). Finally, we found that the risk of CRC due to meat consumption differed between men and women, as has been noted previously (Pietinen et al., 1999).

In conclusion, we found a significant positive association between meat consumption and the risk of CRC. Although the mechanisms by which the frequency of meat consumption is involved in colorectal carcinogenesis are unclear, restricting meat consumption is considered to be beneficial for preventing CRC.

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