COMMENTARY

The Increasing Incidence of Colorectal Cancer and the Preventive Strategy in Japan

Kiyonori Kuriki, Kazuo Tajima

Abstract

   Background: In Japan, the westernization of lifestyle, especially dietary habits, has progressed remarkably since 1950 and is presumably directly related to the increasing incidence of colorectal cancer (CRC). The aim of this epidemiology note was to summarize the most recent trends in CRC incidence and predictions until 2020 for suggesting the preventive strategies in Japanese. Methods: Using the newest published data in Japan, the most recent trends in CRC incidence and the predicted numbers of incident cases of CRC until 2020 were summarized. Results: Dietary intake of milk, meat, eggs and fat/oil demonstrated remarkable increment through 1950 to 1970, and since then has remained relatively constant. Compared with values for 1975, age-adjusted incidence rates for colon and rectal cancers were estimated to be 3.7 and 1.9 times higher among men and 2.9 and 1.3 times higher among women by 1995 or 2000, respectively, and then to plateau. Considering progression of aging of the society, numbers of incident cases for colon cancer among men and women have been predicted to increase 9.5 and 7.5 times by 2005 and 12.3 and 10.5 times by 2020, respectively, from the 1975 baseline. Likewise, the figures for rectal cancer have been predicted to increase. Conclusion: The increment of CRC incidence is assumed to coincide with such changes in dietary intake after approximately 20-years lag. Concrete programs for lifestyle modification and more emphasis of early cancer screening are now needed for prevention purposes.

Key Words: Colorectal cancer – cancer incidence – cancer prevention – Westernized lifestyle – Japan

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Introduction

   More than 90% of colorectal cancers (CRCs) are sporadic, generated by the accumulation of both genetic mutations and DNA lesions via many gene-environmental interactions, as with neoplasia in other body sites. Approximately 90% of CRCs are adenocarcinomas. Many epidemiological and experimental studies have focused on diet as one important risk factor in the etiology of CRC, and there is a body of evidence that the remarkable increase in incidence in Japan is associated with the westernization of the lifestyle, especially the dietary habits (Tominaga and Kuroishi, 1997). Among Japanese in Japan (J-Japanese), the CRC incidence offers a sharp contrast to the decrease in gastric tumors, similar to the case in descendents of Japanese immigrants in the United States (US-Japanese)(Tajima and Tominaga, 1985b; Waterhouse et al., 1982; Parkin et al., 1992, 2002).

   CRC incidences vary from country to country and over time, reflecting geographical variation and chronological change in food/nutrient intake. Although dietary habits are not as easy to assess accurately as other lifestyle factors such as smoking and drinking, our consumption may be closely related to the complex etiology of CRC. According to data from the National Nutritional Survey, intake of western-type foods, especially milk, meat, eggs and fat/oil, increased through 1950 to 1970, and then remained constant or slightly increased (Figure 1)(Ministry of Health, Labor and Welfare, Division of Health and Nutrition, 1997, 2002; Kuriki et al., 2004b). The intake of rice and potatoes gradually decreased to 50% of the values in 1950, while values for fish, beans, green-yellow vegetables and other vegetables have remained relatively constant. Therefore, modification of our current dietary habits may contribute greatly to primary prevention for CRC.

   Using the newest published data (Waterhouse et al., 1982; Parkin et al., 1992, 2002; Ohno et al., 2004; Kuroishi et al., 2004; The Research Group for Population-based cancer Registration in Japan, 2004), we here summarize the most recent trends in CRC incidence, and the predicted numbers of incident cases of CRC and their rates until 2020 as a basis for suggesting prevention strategies.

Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute,1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
Phone: +81-52-762-6111 Fax: +81-52-763-5233 E-mail: kkuriki@aichi-cc.jp
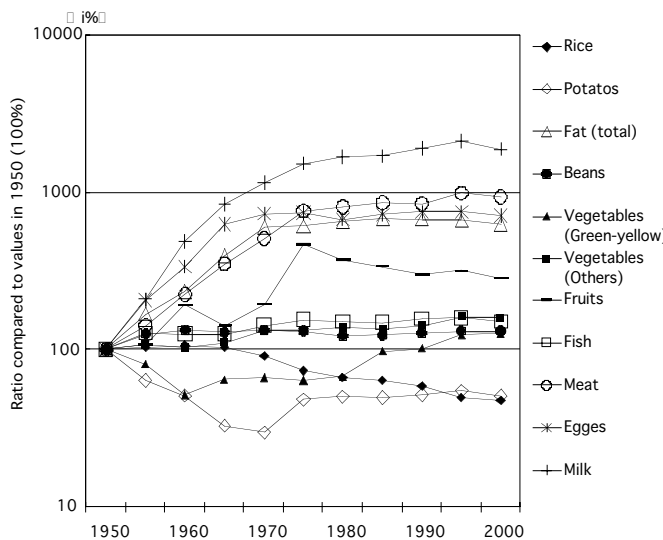
Figure 1. Relative Changes in Selected Food Intake in Japan (1950-2000)

Methodology

The age-adjusted incidence rates (AAIRs, a Japanese population on 1985) and the predicted numbers of the incident cases for CRC [International Classification of Diseases (ICD) 10th] until 2020 were obtained from a book "Gan-Toukei-Hakusho (Incidence/Mortality/Prognosis) 2004" and data according to the Research Group for Population-based Cancer Registration (Ohno et al., 2004). Age-adjusted mortality rates (AAMRs) for CRC (ICD, 9th revision) were obtained from "Gann Monograph on Cancer Research" (Kuroishi et al., 2004). The age-specific incidence rates for CRC were also obtained from "Gann Monograph on Cancer Research" (The Research Group for Population-based cancer Registration in Japan, 2004), but ICD version

was not described in detail. The age-standardized incidence rates (ASIRs, a modified world population) for CRC (ICD, 8th, 9th, 10th) among Japanese in Miyagi and Osaka Prefectures, Japan (J-Japanese), Japanese living in Los Angeles (US-Japanese) and non-Hispanic Whites living in Los Angeles (US-Whites) were based on data from "Cancer Incidence in Five Continents" (Waterhouse et al., 1982; Parkin et al., 1992, 2002). With reference to changes in food intake since 1950 (Figure 1) (Ministry of Health, Labor and Welfare, Division of Health and Nutrition, 1997, 2002; Kuriki et al., 2004b), the most recent trends in CRC incidence, and the predicted numbers of incident cases of CRC and their rates until 2020, the current status of CRC and the prevention strategy are summarized for: 1) time trends; 2) age and gender; 3) geographic distributions; 4) ethnic variation for J-Japanese, US-Japanese and US-Whites.

CRC Incidence

1) Time trends

AAIRs for CRC, especially for colon cancer, demonstrated significant elevation in both genders until 1995 (Figure. 2). In 2000, AAIRs for colon and rectal cancers were estimated to be the third and the sixth most common among men, and the fourth and the sixth among women. Overall, AAIRs for CRC accounted for 16.7% (the second) and 15.7% (the second) of all sites for men and women, respectively. Compared with values for 1975, AAIRs for colon cancer by 2000 had increased 3.9 times for men and 2.9 times for women, and the Research Group for Population-based Cancer Registration in Japan predicts that they will remain at a plateau until 2020. Likewise, AAIRs for rectal cancer by 2000 had increased 2.0 and 1.4 times for men and women, respectively, and they are also predicted to remain at a plateau until 2020. The predicted AAIRs for CRC in 2020 are 17.4% (the second) and 16.2% (the third) of all
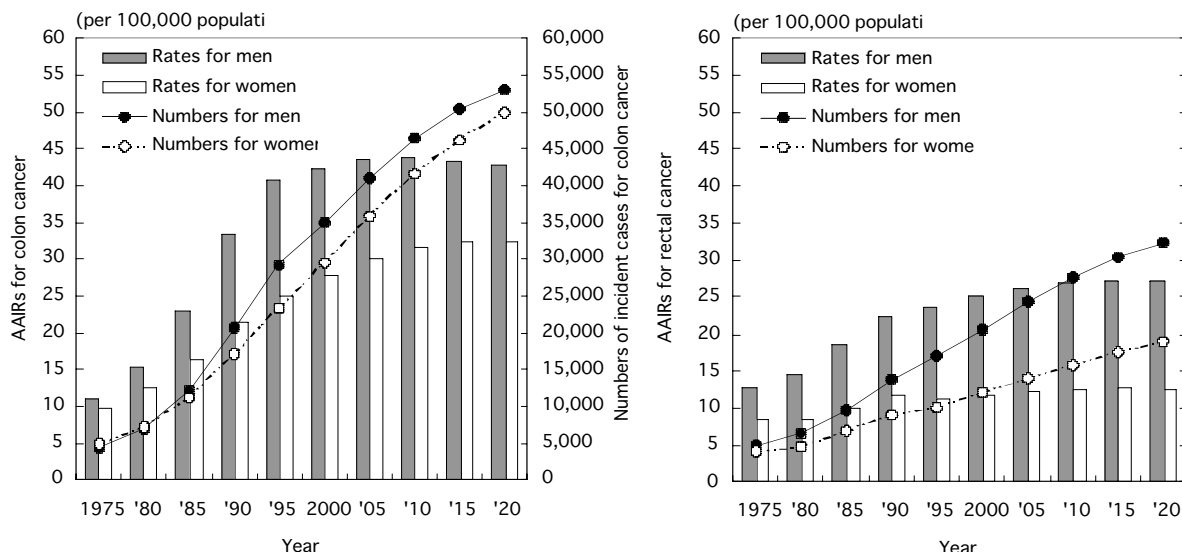
Figure 2. Time Trends in Age-adjusted incidence Rates (AAIRs) and Numbers of Incident Cases for Colon (left) and Rectal (right) Cancers in Japan by Gender

sites among men and women, respectively, but those may have been underestimated due to the gentle increase in slope just before the estimation. On the other hand, in 2000, CRC was also the fourth (11.2%) and the second (13.2%) leading cause of cancer death among men and women. AAMRs for colon cancer in men have been increasing, while those in women have been gradually decreasing.

The rate for patients aged over 70 years out of all incident cancer cases was 47.3% (270,905 / 572,564) in 2000 and will be 63.8% (544,606 / 853,963) in 2020. The increment in patients aged over 70 years (from 270,905 to 544,606) is estimated to be much greater than that for all incident cancer cases (from 572,564 to 853,963). Considering progression of the aging of society, therefore, it can be estimated that numbers of incident cases for colon cancer in 2005 and 2020 will increase 9.5 and 12.3 times among men and 7.5 and 10.5 times among women, respectively, compared with values in 1975 (Figure 2). For rectal cancer the values are 4.9 and 6.5 times in men and 3.4 and 4.6 times in women, respectively. The estimated numbers of incident cases for CRC in 2020 are 17.0% (the second) and 19.5% (the first) of all sites among men and women, respectively.

Time-series analyses indicate that ratios of fat/total

dietary fiber intake through 1947 to 1987 had the highest positive correlation with the AAMR for colon cancer after 16-years delay (Tsuji et al., 1996). A recent birth cohort analysis based on data from 1950 to 1998 in Japan revealed an annual increment of AAMR for CRC (Nakaji et al., 2003), but the prognosis is rather better than with many other cancers. On the other hand, our findings based on Figures 1 and 2 provide support for the hypothesis that the increment pattern in time trend of AAIRs for CRC might coincide with the changes of dietary habit observed 20 years earlier (Kono, 2004). Further observations and analyses, therefore, are necessary to investigate the relationship between foods/ nutrients and CRC incidence, assuming an appropriate time- lag, and considering also smoking and drinking habits and improvement in cancer diagnostic and therapeutic techniques (Tominaga and Kuroishi, 1997).

2) Age and gender

CRC incidence increases with advancing age, although a shift to younger age, dramatically, has been found with the exception of 1995 to 1998 (Figure. 3). CRCs occur more frequently among men than among women, with sex ratios for the colon and rectum of 1.1 and 1.5 in 1975, 1.4 and 1.8
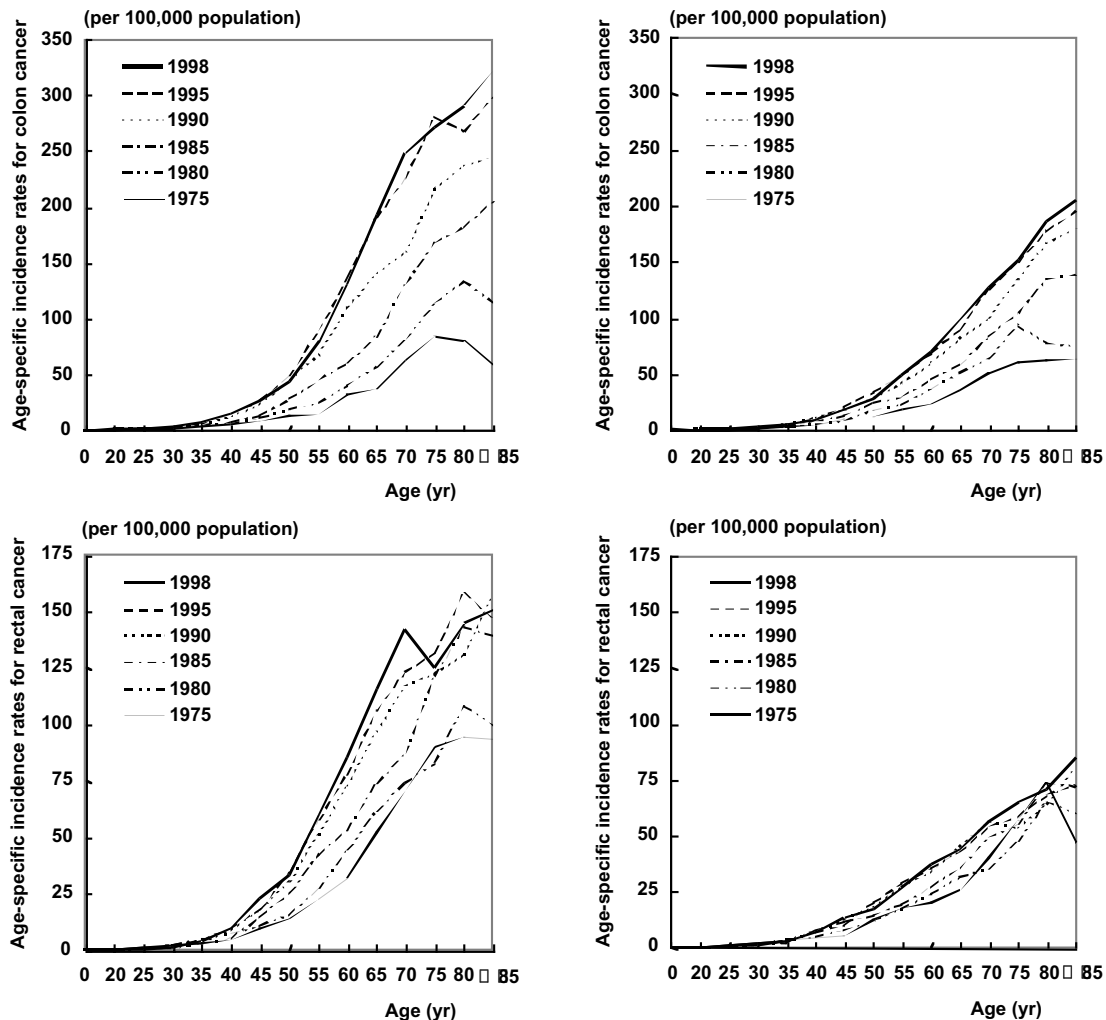

Figure 3. Age-specific Incidence Rates for Colon (upper) and Rectal (lower) Cancers in Japan by Gender

in 1985, 1.6 and 2.1 in 1995, and an estimated 1.3 and 2.2 in 2020, respectively (Figure 2). Mortality is higher from colon than rectal cancers, and CRC deaths occur more frequently among men than among women.

3) Geographical differences

In 1993-97, ASIRs for CRC were higher in Miyagi prefecture (North area) than in Osaka prefecture (Figure. 4). Geographical differences, however, must take into account the data quality for CRC incidence in each area. As available indicators of registration completeness and the validity of the diagnostic information for colon cancer in 1993-97, the percentage of cases with diagnosis based on death certificate information only (DCO), the ratio of mortality versus incidence registered (MI), and the percentage of cases with morphological verification of diagnosis (MV) among both genders were as follows; 6-8%, 49-53% and 75-78% for Osaka prefecture, 9-14%, 33-42% and 82-87% for Miyagi prefecture, respectively. The AAMRs for colon cancer in the 1970s were higher in urban than rural areas (Tajima and Tominaga, 1985a), but AAMRs for CRC in 2000 were also higher in the North, without major cities, than in other areas of Japan. In metropolitan cities, values were highest, albeit only slightly.

4) Variety among ethnic groups

Epidemiological studies of immigrants are very important for determination of host and environmental factors. Until the 1980s, ASIRs for CRC among US-Japanese were higher than those among J-Japanese, and were almost the same or slightly higher than those among US-Whites. In 1993-97, however, ASIRs for colon cancer among J-Japanese men (in Miyagi prefecture) were the highest among the ethnic male groups, and those for CRC were almost the same between J-Japanese and US-Japanese (Figure. 4). In various ethnic groups who live in Los Angeles (Waterhouse et al., 1982; Parkin et al., 1992, 2002), ASIRs for colon cancer were the highest among US-Blacks, but those for both rectal cancer and CRC in total were highest among US-Japanese. In sharp contrast to the increment of ASIRs for CRC among J-Japanese, among US-Whites gradual reduction has been observed, decade by decade. Among US-Japanese men and women, ASIRs for colon cancer in 1993-97 were also decreased, as compared to the 1987-93 period. Japan, therefore, is now one of highest countries with regard to the CRC incidence. Likewise, the indices of DCO, MI and MV for various ethnic groups should be took into account; 0%, 35-36% and 98-99% for US-Japanese; 1-2%, 38-40 and 97-98% for US-Whites; and 1%, 43-44 and 96-98% for US-Blacks, respectively. Comparing with the Japanese and American diets, the amount of fat intake (energy intake, %) and the ratios of saturated fatty acids: monounsaturated fatty acids: polyunsaturated fatty acids are 40-50g (20-25%) and 1: 1: 1, and 80-90g (35-40%) and 2: 2: 1, in that order, and
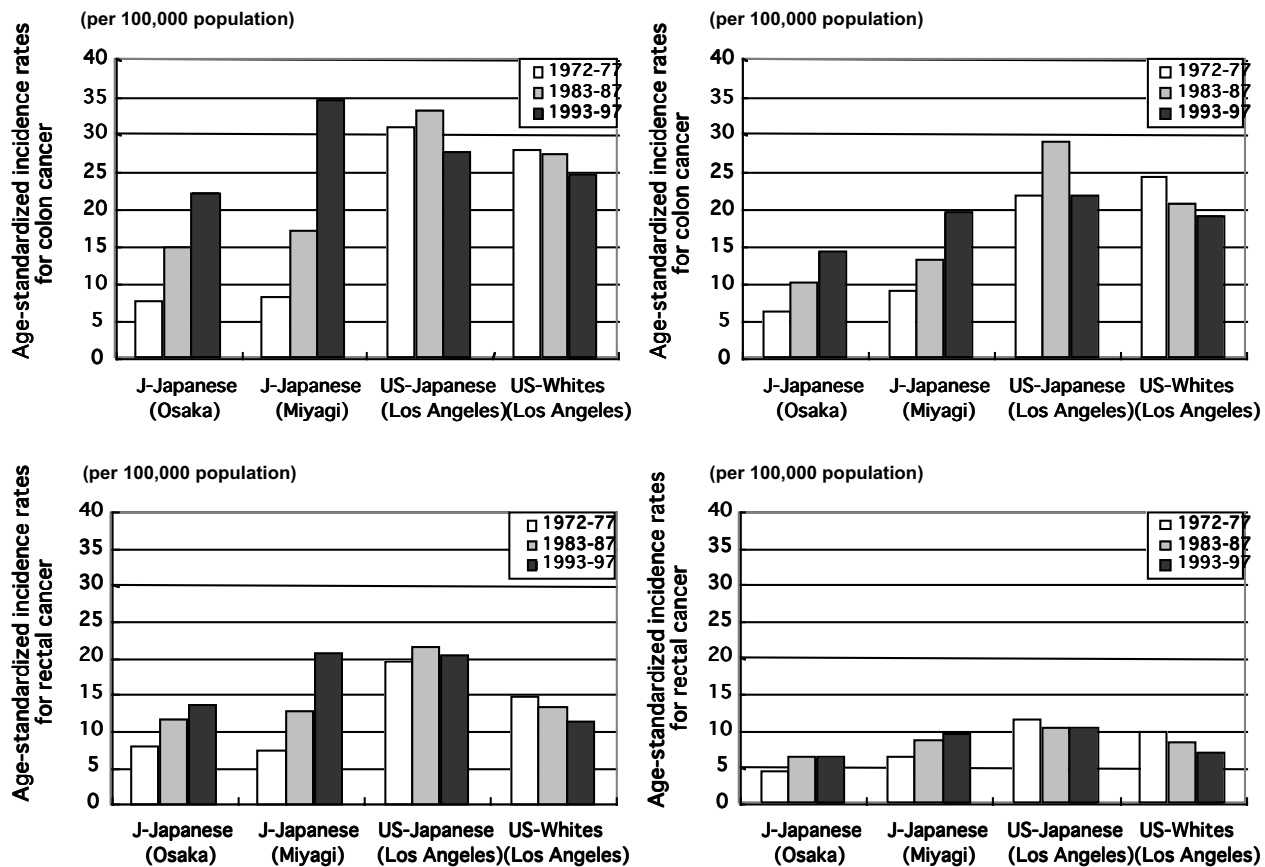

Figure 4. Age-standardized Incidence Rates (ASIRs) for Colon (upper) and Rectal (lower) Cancer among J-Japanese, US-Japanese and US-Whites by Gender

this diversity may be closely related to CRC (Tokudome et al., 2000).

Preventive Strategies for CRC

Primary prevention for CRC, such as lifestyle modification with regard to food/nutrient consumption, alcohol drinking and smoking habits and habitual exercise, is of great consequence. In 1997, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/ AICR) suggested the following: 1) the most effective ways to prevent CRC are to intake diets high in vegetables (not including fruits), undergo regular exercise (for colon cancer), and reduce consumption of red and processed meat; 2) possible further means of CRC prevention are maintenance of suitable body weight for each individual and consumption of diets rich in non-starch polysaccharides (fiber), starch and carotenoids derived from plants, and low in sugar, total fat, saturated (animal) fat, heavily cooked meat and eggs; and 3) frequent eating is also one possible risk factor (WCRF/ AICR, 1997). The risk and protective factors for CRC in a Japanese population are summarized in Table 1 (WCRF/ AICR, 1997; The Japanese Society of Cancer Epidemiology, 1998).

The most recent reports in Japan failed to find any associations between CRC risk and high consumption of fat and meat, or low intake of vegetables/fruit and dietary fiber (Kobayashi et al., 2004; Kojima et al., 2004). As a biomarker of fish consumption, however, high levels of docosahexaenoic acid in serum and erythrocytes are associated with decreased CRC risk (Kojima et al., 2005; Kuriki et al., 2006c). Although the evidence that smoking increases CRC risk is equivocal, it is reported to increase the risk of colorectal adenomas, obesity and type 2 diabetes, the latter demonstrating dramatic increase among J- and US-Japanese with the westernization of lifestyle (Kuriki et al., 2004a; 2005; 2006b). Indeed type 2 diabetes and insulin resistance have been suggested to be associated with an increasing risk for CRC because insulin plays roles in cell proliferation, transformation, p53-dependent apoptosis and bioavailability of insulin growth factor-I (Kuriki et al., 2004; 2006b).

Table 1. Risk and Preventive Factors of Colorectal Cancer Judged by World Cancer Research Fund/American Institute for Cancer Research for a World Population and the Japanese Society of Cancer Epidemiology for a Japanese Population[1-4]

Risk and preventive factors[1]	Judgements for the world population[2]	Judgements for the Japanese population[3]
Common for all of sites		
Risk factors		
Passive smoking	Possible	Possible
Excessive drinking	Probable	Possible
Excessive intake of salt, salting	No description	Possible
Excessive intake of fat/oil, meat	Probable	Possible
Excessive intake of grilled meat, fish	Possible	Impossible[4]
Physical inactivity	Convincing (Colon)	Probable
	No judgement (Rectum)	
Obesity or over weight	Possible	Impossible[4]
Protective factors		
Vegetables, Fruit	Convincing	Probable
Green-yellow vegetables	Possible	Probable
Foods rich in dietary fiber	Possible	Probable
(e.g., Beens, Grain/Cereals and Seaweeds)		
Green tea	No description	No judgement
Specific for colon and rectum		
Risk factors		
Ulcerative colitis	Convincing	No judgement
Schistoma sinesis[5]	Convincing	Impossible[4]
Inheritance	Convincing	Convincing
Frequent eating	Possible	No judgement
Protective factors		
Aspirin	Convincing	No judgement

[1]Judgments were graded according to the strength of the evidence; convincing, probable, possible and (insufficient), in that order. Considering lifestyle and host factors in a Japanese population, moreover, several risk and protective factors were jugged by the grad including "no description", "no judgment" and "impossible". [2]Judged by World Cancer Research Fund/American Institute for Cancer Research. [3]Judged by the Japanese Society of Cancer Epidemiology. [4]Although there was little study to clarify relationships between increased or decreased risk and the factors in a Japanese population, the grade "impossible" was defined as possible risk or protective factors for the population according to the Japanese Society of Cancer Epidemiology. [5]"Schistosoma sinensis" was described World Cancer Research Fund, but "Schistosoma japonicum" may be correct.

A large number of clinical trials with chemoprevention drugs have demonstrated to reduce the size and number of colorectal polyps by non-selective cyclooxygenase inhibitors such as aspirin and piroxicam, but their efficacy is still insufficient for clinical apply due to their side effects (Ishikawa et al., 2004). Recently, cerecoxib, which is one of selective cyclooxygenase-2 inhibitors, has also been reported to increase the risk of serious cardiovascular events during a clinical trial for colorectal adenoma prevention (Solomon et al., 2005). For Japanese with familial risks of CRC, administration of supplemental dietary fiber was unfortunately observed no association with the recurrence of colorectal tumors, whereas *Lactobacillus casei* intake appeared to reduce the development of tumors with moderate and severe atypia (Ishikawa et al., 2005). Dietary Intervention to Polypectomized Patients Study is now on going to clear a reduced risk of colorectal adenomas/tumors according to an elevated intake of fish, perilla oil and n-3 polyunsaturated fatty acids (Tokudome et al., 2002; Cheng et al., 2003).

From recent results of gene-environmental interactions among J-Japanese, gene polymorphisms in the following enzymes have been demonstrated to increase CRC risk: 1) alcohol dehydrogenase and aldehyde dehydrogenase 2 for alcohol metabolism (Matsuo et al., 2002); 2) methylenetetrahydrofolate reductase for metabolism of folic acid rich in rice and green leaf vegetables among heavily drinkers (Ying et al., 2004); and 3) CD36 (long-chain fatty acid translocase/oxidized low-density lipoprotein scavenger) for fat/lipid metabolism according to meat or saturated (animal) fat consumption and peroxisome proliferator-activated receptor gamma (PPARg)(Kuriki et al., 2004a; 2005; 2006a). In the future, it should be possible to stratify individuals with inherent genetic predispositions as of high risk, to facilitate development of strategies for CRC prevention.

For secondary CRC prevention, cancer screening was begun by the support of Japanese government in 1983, and has been transferred to local government since 1998. CRC has been covered for persons aged 40 years or older since 1992 and this screening was fair evidence for reduction in mortality form CRC (a two-day immunochemical fecal occult blood test) (Saito, 2000). Persons with positive reactions on this first test followed to take barium enema or/and endoscopy, but the compliance with work-up examinations was only 60% due to insufficient information or knowledge about this screening program. More than 4 million persons are reported to take this screening program in 1995, but those were too low for target population. In the report, positive results of the first test were obtained in about 7% (at least 6,500 cases) of the screenees, and, simultaneously, a positive predictive value for cases was calculated to be 3.4% when the number of them undergoing diagnostic examination was used as a denominator.

Conclusions

Since 2004, the Japanese government has projected the 3rd Term Comprehensive 10-Year-Strategy for Cancer Control and aimed at reducing both cancer incidence and mortality in all sites. The present discussion of possible associations between the increasing incidence of CRC and westernized dietary habits in Japan, provides additional evidence of the importance of modifying our current dietary habits for preventing CRC, along with massive cancer screening.

Acknowledgments

References

Cheng J, Ogawa K, Kuriki K, et al (2003). Increased intake of n-3 polyunsaturated fatty acids elevates the level of apoptosis in the normal sigmoid colon of patients polypectomized for adenomas/tumors. *Cancer Lett*, **193**, 17-24.

Ishikawa H (2004). Chemoprevention of carcinogenesis in familial tumors. *Int J Clin Oncol*, **9**, 299-303.

Ishikawa H, Akedo I, Otani T, et al (2005). Randomized trial of dietary fiber and *Lactobacillus casei* administration for prevention of colorectal tumors. *Int J Cancer*, **116**, 762-7.

The Japanese Society of Cancer Epidemiology. Seikatsu-shukan to Shuyou-bui no gan: World Cancer Research Fund/American Institute for Cancer Research ed. "Food, Nutrition and the Prevention of Cancer" no Nippon-jin heno tekiyo. pp14-21. Fukuoka: Kyushu Daigaku Shuppan-kai, 1998 (in Japanese).

Kobayashi M, Tsubono Y, Otani T, et al (2004). Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. *Nutr Cancer*, **49**, 32-40.

Kojima M, Wakai K, Tamakoshi K, et al (2004). Diet and colorectal cancer mortality: results from the Japan Collaborative Cohort Study. *Nutr Cancer*, **50**, 23-32.

Kojima M, Wakai K, Tokudome S, et al (2005). Serum levels of polyunsaturated fatty acids and risk of colorectal cancer: a prospective study. *Am J Epidemiol*, **161**, 462-71.

Kono S (2004). Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*, **13**, 127-32.

Kuroishi T, Hirose K, Takezaki T, Tominaga S, Tajima K (2004). Cancer mortality in Japan (1950-2000). *Gann Monogr Cancer Res*, **51**, 1-93.

Kuriki K, Hamajima N, Chiba H, et al (2004a). Increased risk of colorectal cancer by the interaction between meat consumption and the CD36 gene A52C polymorphism among Japanese. *Nutr Cancer*, **51**, 170-7.

Kuriki K, Tokudome S, Tajima K (2004b). Association between type II diabetes and colon cancer among Japanese with reference to change in food intake. *Asian Pacific J Cancer Prev*, **5**, 28-35.

Kuriki K, Hamajima N, Chiba H, et al (2005). Relation of the CD36 gene A52C polymorphism to the risk of colorectal cancer among Japanese, with reference to with the aldehyde dehydrogenase 2 gene Glu487Lys polymorphism and drinking habit. *Asian Pac J Cancer Prev*, **6**, 62-8.

Kuriki K, Hirose K, Matsuo K, at al (2006a) Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARg gene and colorectal cancer risk in Japanese. Cancer Sci, (in press).

Kuriki K, Hirose K, Tajima K (2006b). Diabetes and cancer risk for all and specific sites among Japanese men and women. *Eur J Cancer Prev*, (in press).

Kuriki K, Wakai K, Hirose K, et al (2006c). Risk of colorectal cancer is linked to erythrocyte compositions of fatty acids as biomarkers for dietary intakes of fish, fat and fatty acids. *Cancer Epidemiol Biomarkers Prev*, (in press).

Matsuo K, Hamajima N, Hirai T, et al (2002). Aldehyde dehydrogenase 2 (ALDH2) genotype affects rectal cancer susceptibility due to alcohol consumption. *J Epidemiol*, **12**, 70-6.

Ministry of Health, Labor and Welfare, Division of Health and Nutrition (1999, 2002). Kokumin-Eiyo-no-Genjo (Current Status of National Nutrition). Tokyo: Dai-ichi Shuppan, 1997, 2002 (in Japanese).

Nakaji S, Umeda T, Shimoyama T, et al (2003). Environmental factors affect colon carcinoma and rectal carcinoma in men and women differently. *Int J Colorectal Dis*, **8**, 481-486.

Ohno Y, Nakamura T, Murata K, Tsukuma H, Ajiki W, Oshima A. Nipponn-no-Gan-Rikan-no-Shourai-Suikei. In: Oshima A, Kuroishi T, Tajima K, eds. Gan-Toukei-Hakusho (Incidence/Mortality/Prognosis) 2004. pp201-17. Tokyo: Shinohara Shuppan, 2004 (in Japanese).

Parkin DM, Muir CS, Whelan SL, et al (1992). Cancer Incidence in Five Continents VI, No.120. Lyon: IARC.

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2002). Cancer Incidence in Five Continents VIII, No.155. Lyon: IARC.

The Research Group for Population-based cancer Registration in Japan (2004). Cancer Incidence in Japan. *Gann Monogr Cancer Res*, **51**, 95-130.

Saito H (2000). Screening for colorectal cancer: current status in Japan. *Dis Colon Rectum*, **43**, S78-84.

Solomon SD, McMurray JJ, Pfeffer MA, et al (2005). Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*, **352**, 1071-80.

Tajima K, Hirose K, Nakagawa N, Kuroishi T, Tominaga S (1985a). Urban-rural difference in the trend of colorectal cancer mortality with special reference to the subsites of colon cancer in Japan. *Jpn J Cancer Res (Gann)*, **76**, 717-28.

Tajima K, Tominaga S (1985b). Dietary habits and gastro-intestinal cancers: A comparative case-control study of stomach and large intestinal cancers in Nagoya. Japan. *Jpn J Cancer Res (Gann)*, **76**, 705-16.

Tokudome S, Nagaya T, Okuyama H, et al (2000). Japanese versus Mediterranean Diets and Cancer. *Asian Pac J Cancer Prev*, **1**, 61-6.

Tokudome S, Yokoyama Y, Kamiya T, (2002). Rationale and study design of dietary intervention in patients polypectomized for tumors of the colorectum. *Jpn J Clin Oncol*, **32**, 550-3.

Tominaga S, Kuroishi T (1997). An ecological study on diet/nutrition and cancer in Japan. *Int J Cancer*, **10**, S2-6.

Tsuji K, Harashima E, Nakagawa Y, Urata G, Shirataka M (1996).

Time-lag effect of dietary fiber and fat intake ratio on Japanese colon cancer mortality. *Biomed Environ Sci*, **9**, 223-8.

Waterhouse J, Muir C, Shanmugaratnam K, Pauell J (1982). Cancer Incidence in Five Continents IV, No.42. Lyon: IARC, .

World Cancer Research Fund/American Institute for Cancer Research (1997). Food, Nutrition and the Prevention of Cancer: a Global Perspective, pp216-251, Washington DC, AI CR.

Ying G, Kono S, Toyomura K, et al (2004). Methylene-tetrahydrofolate reductase C677T and A1298C polymorphisms and colorectal cancer: the Fukuoka Colorectal Cancer Study. *Cancer Sci*, **95**, 908-13.