RESEARCH COMMUNICATION

Association between Type II Diabetes and Colon Cancer among Japanese with Reference to Changes in Food Intake

Kiyonori Kuriki[1, 2], Shinkan Tokudome[2], Kazuo Tajima[1]

Abstract

   Many epidemiological studies have provided support for the hypothesis that type II diabetes can increase the risk of colorectal cancer, but time trends, geographical distributions and host factors for the two diseases remain largely to be clarified. To address these issues, we investigated the epidemic pattern of colon cancer and type II diabetes among Japanese in Japan (J-Japanese), with consideration of the westernization of dietary habits. Over the last three decades, the increase in crude mortality rates of colon cancer from the Vital Statistics has closely paralleled the increment in prevalence rates (PRs) from hospital based surveys of diabetes. Age-standardized incidence rates (ASIRs) for colon cancer among Japanese in the United States (US-Japanese) were higher than those among J-Japanese and almost the same as those among US-Whites, while PRs for type II diabetes among US-Japanese were the highest in the three populations. Correlation analysis showed that PRs for type II diabetes had a positive association with ASIRs for colon cancer among the combination of Japanese and US-Japanese (r=0.79, p<0.01). Since 1950, intake of milk, meat, eggs and fat/oil has increased, while that of rice and potatoes has gradually decreased. Our findings indicate that the increment of ASIRs for colon cancer among J-Japanese might be closely associated with the increment of PRs for type II diabetes, reflecting the westernization of food intake.

Key Words: Colon cancer - type II diabetes - food intake - Japanese

Introduction

   In Japan, the westernization of lifestyle, especially dietary habits, has progressed remarkably over the last half century, accompanied by trends for change in age-standardized incidence rates (ASIRs) and age-adjusted mortality rates for gastrointestinal cancers, with the reduction of gastric cancer and the increment in colorectal cancer (Tominaga and Kuroishi, 1997; Tajima and Tominaga, 1985). The Cancer Incidence in Five Continents books published by the International Agency for Research on Cancer/ International Association of Cancer Registries have documented the rapid increase in ASIRs for colon cancer among descendents of Japanese in the United States (US-Japanese) and the gradual reduction in those for stomach cancer among Japanese in Japan (J-Japanese) (Muir et al., 1987; Parkin et al., 1992; 1997).

   Epidemiological studies have suggested that the westernization of lifestyle is also associated with change in prevalence rates (PRs) for type II diabetes (non-insulin dependent diabetes) (Fujimoto, 1992; King and Rewers, 1993; King et al., 1998). In the early 1980s, PRs for type II diabetes among US-Japanese Nisei (second-generation) were four times higher than those among J-Japanese, based on identical diagnostic criteria (Fujimoto, 1994). Among J-Japanese aged over 40 years, furthermore, PR of type II diabetes with glycated hemoglobin (HbA1c >= 6.1%) was estimated to be 8.2% from results of the National Nutritional Survey (Ministry of Health, Labor and Welfare, Division of Health and Nutrition, 1999) conducted in 1997.

[1]*Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681, Japan Tel: +81-52-762-6111; Fax: +81-52-763-5233 E-mail: kkuriki@aichi-cc.jp (KK), ktajima@aichi-cc.jp (KT)* [2]*Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, 467-8601, Japan Tel: +81-52-853-8174; Fax: +81-52-842-3830 E-mail: tokudome@med.nagoya-cu.ac.jp (ST) Correspondence to: Kiyonori Kuriki, Ph.D., Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Kanokoden, Chikusa-ku, Nagoya, 464-8681, Japan Tel: +81-52-762-6111; Fax: +81-52-763-5233; E-mail: kkuriki@aichi-cc.jp*

Since 1970, many studies have provided support for the hypothesis that type II diabetes increases the risk of colorectal cancer, and several authors have speculated possible biological mechanisms, including impaired glucose tolerance (IGT) and insulin resistance (McKeown-Eyssen, 1994; Will et al., 1998; Bruce et al., 2000; Mori et al., 2000; Giovannucci, 2001; Sandhu et al., 2002). However, time trends, geographic distributions and host factors, such as age, gender and ethnic variation, for the two diseases have not well documented with reference to changes in food intake. The purpose of the present study was to clarify these issues, focusing on the association between colon cancer and type II diabetes, using available information published in Japan and the US.

Materials and Methods

Food consumption data for period from 1950 to 2000 in Japan were accessed from the National Nutritional Survey (Ministry of Health, Labor and Welfare, Division of Health and Nutrition, 2002). Crude mortality rates for colon cancer [International Classification of Diseases (ICD), 10th] and PRs from hospital based surveys (PRs-HBS) of diabetes (ICD 9th for 1979-1995 and 10th from 1996) were derived from the Vital Statistics of Japan (Ministry of Health and Welfare of Japan, 1995; 2002). PRs-HBS for diabetes were not adjusted for age and were defined as rates for all clinic patients (out- and in-patients) with diabetes on the National Patient Surveys in 1972, 1980 and 1990 (Ministry of Health and Welfare of Japan, 1974; 1982; 1992). Age-specific mortality rates (ASMRs) for colon cancer (ICD 9th revision) were obtained from the National Statistics of Japan (1950-1995)(Kuroishi et al., 1997).

ASIRs for colon cancer were obtained from the Cancer Incidence in Five Continents Vols. VI and VII (ICD 9th)(Parkin et al., 1992; 1997). Among J-Japanese, the cancer registries from Osaka prefecture in 1988-92, Tohoku area (Yamagata prefecture) in 1988-92 and Kyushu area (Saga prefecture in 1988-92 were corresponded to the below study locations and the periods for type II diabetes, respectively (Figure 1). Likewise, ASIRs among US-Japanese and US-Whites were derived from information as follows; Hawaii and Los Angeles in 1983-87 and 1988-92 for US-Japanese, and Hawaii and Los Angeles, where the majority of US-Japanese live, in 1983-87 and 1988-92 for US-Whites (non-Hispanic Whites), respectively.

PRs for type II diabetes and IGT were derived from Medline-accessed papers, and conducted by large-scale population-based studies (Hara et al., 1994; Harris et al., 1998; Terao et al., 1997). Study location and the periods for type II diabetes and IGT among J-Japanese were as follows; Osaka prefecture in 1992, Tohoku area (Yamagata prefecture) in 1990 and Kyushu area (Fukuoka prefecture) in 1992, respectively (Figure 1). Those rates were adjusted for the Japanese standard population. With regard to ethnic variation, PRs for type II diabetes among US-Japanese and US-Whites were as follows: Hawaii and Los Angels in 1978-

88 for US-Japanese, and the third National Health and Nutrition Examination Survey in 1988-94 for US-Whites, respectively. PRs for IGT among US-Japanese and US-Whites were unobtainable. Age of study subjects, methods of oral glucose tolerance test (OGTT) and the diagnostic criteria for type II diabetes and IGT among J-Japanese, US-Japanese and US-Whites were summarized as follows; >= 40-79y, 75g OGTT, World Health Organization (WHO) for J-Japanese; >=40y, 50g OGTT, the Japan Diabetes Society for US-Japanese in Hawaii; >=40y, 75g OGTT, WHO for US-Japanese in Los Angeles; 40-74y, 75g OGTT, WHO for US-Whites, respectively.

With reference to changes in food intake since 1950, we described the pattern of both colon cancer and type II diabetes since 1970s focusing on issues as follows: 1) time trends; 2) age and gender specificities; 3) geographic distributions; and 4) ethnic variation among J-Japanese, US-Japanese and US-Whites, 5) correlation between colon cancer and type II diabetes. Correlation analysis was performed with the PC-SAS statistical package version 8.1 (SAS Institute IN., Cary, NC, USA).

Results

Food intake in Japan increased most for milk from 1950 to 2000, followed by meat, eggs, fat/oil and fruit, while those of rice and potatoes gradually decreased (Figure 2). Westernized food intake, especially milk, meat, eggs and fat/oil, was increased 5 times or more until 1970, and then maintained up to today or further slightly increased. The intake of rice and potatoes was two-third and half fold decreased in 1975, respectively, but that of fish, beans, green-
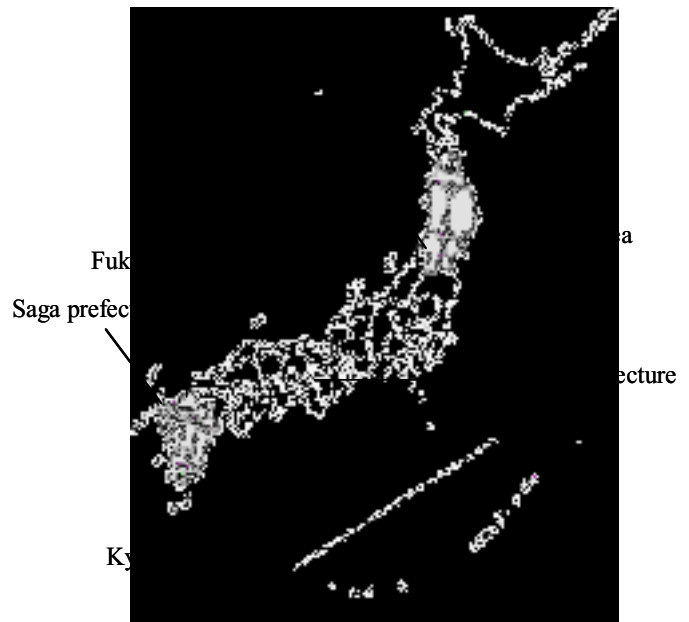
Figure 1. Location of the Representative Areas for Information of Cancer Registries and Data of Type II Diabetes According to Large-scale Population-based Studies in Japan
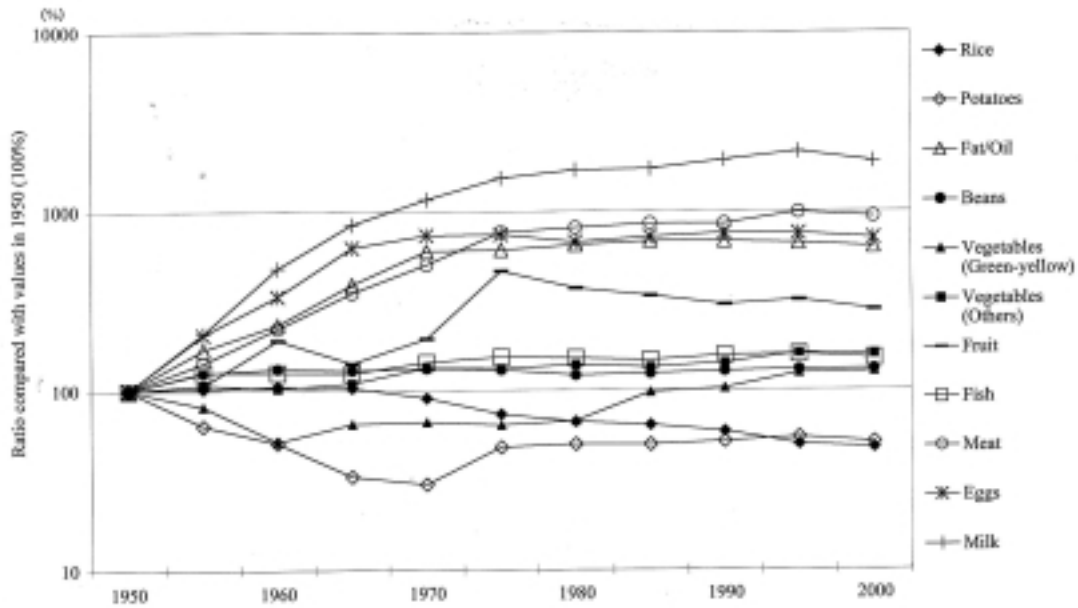
Figure 2. Relative Changes in Selected Food Intake in Japan (1950-2000), Compared with Values for 1950

yellow vegetables and other vegetables remained relatively constant.

Crude mortality rates for colon cancer from 1970 to 2000 among J-Japanese demonstrated 5 and 4.5 fold elevations for men and women, compared with each baseline value,

respectively (Figure 3). PRs-HBS for diabetes similarly increased 2-3 times. The rates in 1996 were slightly decreased because of the alteration of ICD from 9th to 10th. Among men and women, ASMRs for colon cancer had gradually increased with age until 1972, followed by rapid
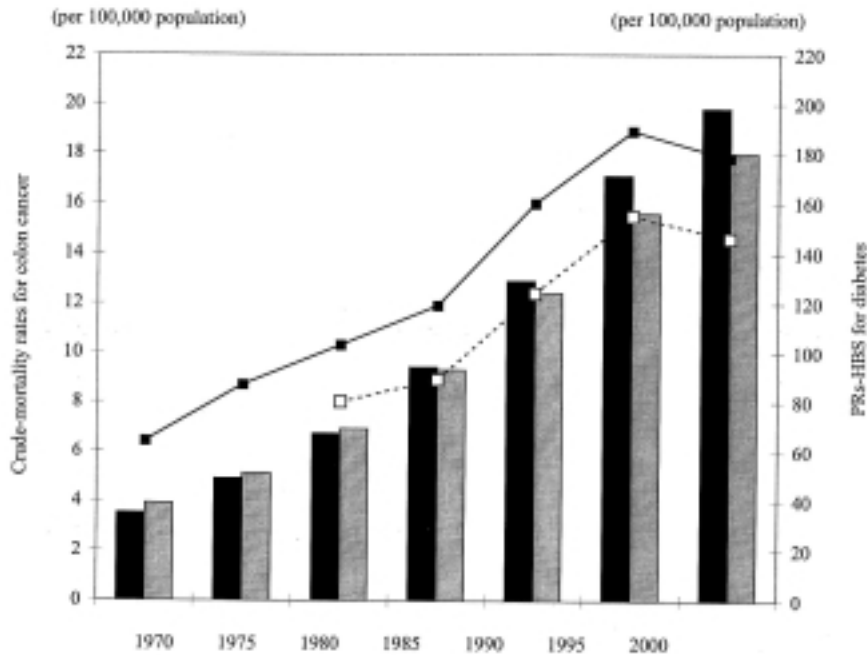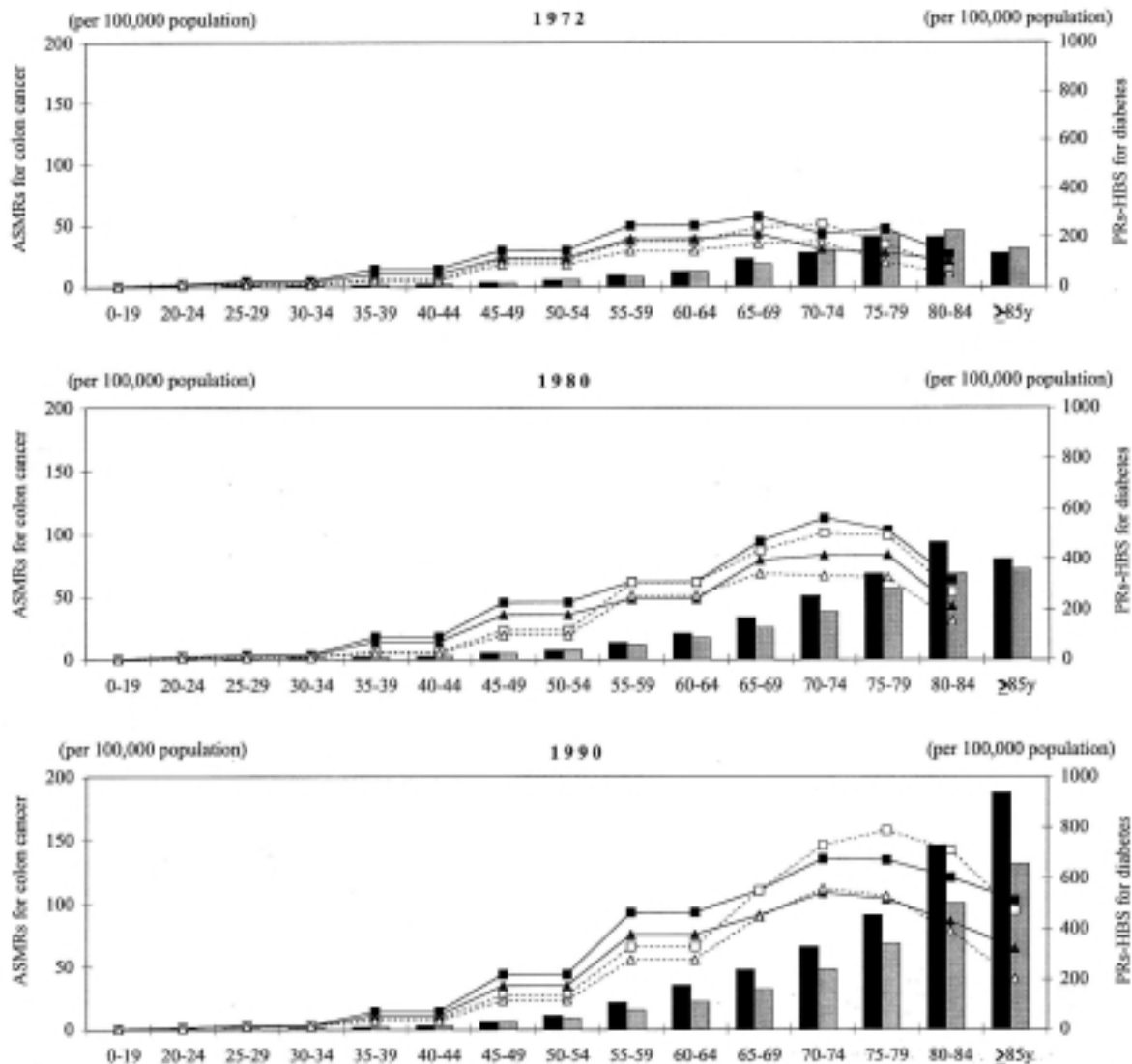

Figure 3. Time Trends in Crude Mortality Rates for Colon Cancer and Prevalence Rates from Hospital Based Surveys (PRs-HBS) for Diabetes among Japanese in Japan, 1970-2000

Colon cancer according to the Vital Statistics of Japan was categorized by ICD 10th. Diabetes was also categorized by ICD 9th from 1979 and 10th from 1996. PRs-HBS for diabetes were defined as rates of all clinic patients (out- and in-patients) with diabetes on the survey day of the National Patient Surveys. PRs-HBS for diabetes were included type I and not separated by gender. Theses two rates were not adjusted for age.

elevation until 1980 and further steep increase in 1990 (Figure 4). ASMRs for colon cancer were increased among both genders aged over 45-49y, and those in 1990 were greater among men than among women. As well as ASMRs for colon cancer, PRs-HBS for diabetes among both genders were rapidly increased with age decade by decade. Among men and women, PRs-HBS for diabetes were significantly increased through 45-49y to 70-74y and 75-79y, respectively, but reduced among those who were more elderly. In 1990, PRs-HBS for diabetes among women aged 70-74y, 75-79y and 80-84y were higher than those among the corresponding men, but overall they were higher among men.

Figure 5 shows a relation between PRs for type II diabetes and ASIRs for colon cancer among J-Japanese and US-Japanese. In early 1990s, geographical differences in Japan were observed that PRs for type II diabetes were the highest in Kyushu area, but ASIRs for colon cancer, especially for women, were the highest in Tohoku area. Whereas, PRs for IGT among J-Japanese men were higher in Kyushu area and Osaka prefecture, but those among J-Japanese women were higher in Kyushu and Tohoku areas (data not shown). Correlation analysis showed that PRs for type II diabetes among the combination of Japanese and US-Japanese had a positive association with ASIRs for colon cancer (r=0.79, p<0.01).

Figure 4. Age-specific Mortality Rates (ASMRs) for Colon Cancer and Prevalence Rates from Hospital Based Surveys (PRs-HBS) for Diabetes among Japanese in Japan by Gender in 1970, 1980 and 1990
Colon cancer was defined by ICD 9th revision. PRs-HBS for diabetes were defined as rates of all clinic patients (out- and in-patients) with diabetes on the survey day of the National Patient Surveys. Type I and II diabetes was not distinguished, and diabetes was defined by ICD 9th in 1980 and 1990.

(per 100,000 population)
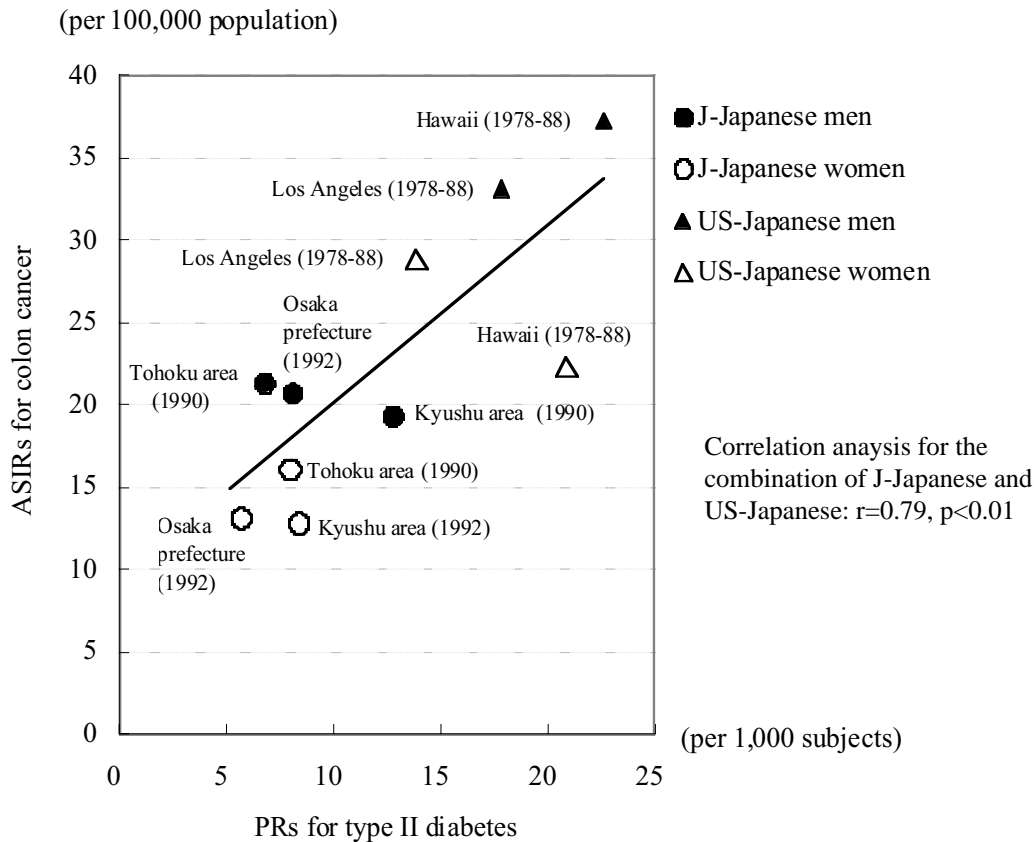
Figure 5. Relation between Prevalence Rates (PRs) for Type II Diabetes and Age-standardized Incidence Rates (ASIRs) for Colon Cancer among Japanese in Japan (J-Japanese) and in the United States (US-Japanese)
ASIRs for colon cancer were adjusted for the world standard population, but PRs for type II diabetes were not done. Figures in parentheses were each study year or period investigated on PRs for type II diabetes, while the corresponding information of ASIRs for colon cancer was as follows: Osaka, Saga and Yamagata prefectures (1988-92) for Osaka prefecture (1992) and Kyushu (Fukuoka prefecture in 1990) and Tohoku areas (Yamagata prefecture in 1992) among J-Japanese, and Hawaii and Los Angeles (1983-87) for same locations (1978-88) among US-Japanese, respectively. Colon cancer was defined by ICD 9th in 1983-87 and 1988-92.

Regarding ethnic variation, ASIRs for colon cancer among US-Japanese were almost the same as those among US-Whites [26.7 and 28.9, and 20.6 and 20.6 per 100,000 population for US-Japanese and US-Whites men and the corresponding women living in Los Angeles (1988-92), in that order]. Furthermore, PRs for type II diabetes among US-Japanese were the highest in three populations including US-Whites [13.4 per 1,000 subjects for both genders (1988-94)]. With elevating PRs for type II diabetes, ASIRs for colon cancer among J-Japanese and US-Japanese have been increased, in contrast to changeless or a little reduction of later rates among US-Whites (Data not shown).

Discussion

Although previous studies have suggested that type II diabetes may be a risk factor for colorectal cancer, the epidemic feature of the two diseases have not well documented simultaneously. Here, we described time trends, geographical distributions and host factors, such as age, gender and ethnic variation for both colon cancer and type II diabetes among J-Japanese. A major strength of this study

was made allowance for significant changes in food intake among J-Japanese, because dietary habits are clearly very important environmental factors determining risks of colon cancer and type II diabetes.

Time Trends
Among J-Japanese men and women, colorectal cancer is the fourth (11%) and the second (16%) leading cause of cancer deaths, respectively. ASIRs for colorectal cancer are accounted for 16-17% of all sites and have been elevated among both genders, and especially those for colon cancer are significantly increased for the latest three decades. Regarding food consumption among J-Japanese, dietary intake of milk, meat, eggs and fat/oil had remarkably increased through 1950 to 1970, and then has remained constant. We, therefore, thought that the increment of colon cancer might have a positive causal association with the remarkable changes in food intake. Time-series analysis showed that ratios of fat/total dietary fiber intake through 1947 to 1987 had a highest positive correlation with age-adjusted mortality rates for colon cancer after 16-years delay (Tsuji et al., 1996).

PRs-HBS for diabetes has been increasing abreast with crude mortality rates for colon cancer. Although PRs for type II diabetes may be underestimated because of the lack of an established method to detect this disease readily in large-scale population-based survey, values in 1990 were elevated three times compared with those in 1970. From results of polynominal regression analyses, PRs for type II diabetes in 1970, 1980 and 1990 were estimated to be 16, 27 and 60 per 1,000 population and 9, 16 and 40 per 1000 population among J-Japanese men and women, respectively (Islam et al., 1999). We have to pay enough caution that PRs for type II diabetes and IGT were not adjusted for the world standard population, and diagnostic criteria for type II diabetes were not unified.

Age and Gender

The incidence rates for colon cancer increase with advancing age. ASMRs for colon cancer have increased, especially among both men and women aged over 45-49y. Age for colon cancer incidence has shown a tendency to shift the younger age decade by decade. Colon cancer occurs more frequently among men than among women, and sex ratios for colon cancer incidence were 1.2 in 1970s, 1.5 in 1980s and 2.0 in 1990s, respectively. Although there is not sufficient information on age-specific PRs for type II diabetes, considerable increase has been reported in individuals older than 45y, with a peak at 65-69y to 70-74y (Kuzuya et al., 1994). PRs for type II diabetes were higher among men than among women, but in 1990, those were higher among women aged 70-74y, 75-79y and 80-84y than among the corresponding men.

Geographical Differences

From 1969 to 1981, age-adjusted mortality rates of colon cancer, especially for men, were higher in urban areas than in rural areas in line with more rapid change in lifestyle in city communities (Tajima et al., 1985). Recently, ASIRs for colon cancer in Tohoku and Kyushu areas have become the same or rather higher than those in Osaka prefecture, because the food consumption among J-Japanese has become westernized throughout the country and previous geographical differences have disappeared. Data conducted from the National Nutritional Survey has shown that regional differences for food consumption in Japan were diminished year by year. ASIRs for colon cancer, however, were slightly higher in metropolitan cities than in other areas (data not shown). Regarding available indicators of registration completeness and the validity of the diagnostic information for colon cancer in 1988-92, the percentage of cases with diagnosis based on death certificate information only, the ratio of death versus incidence registered, and the percentage of cases with morphological verification of diagnosis among both genders were as follows; 8-10%, 47-54 and 73-76% for Osaka prefecture, 15-19%, 49-59 and 63-70% for Saga prefecture, 9-11%, 43-47 and 78-83% for Yamagata prefecture, 0%, unobtainable and 95-98% for US-Japanese in Los Angeles, and 1%, 48 and 96-98% for US-Whites in

Los Angeles, respectively (Parkin et al., 1997). Like ASIRs for colon cancer, PRs for type II diabetes and IGT have been increased in all areas of Japan, but the validity of the diagnostic information for type II diabetes were adequately not evaluated.

Varieties among Ethnic Groups

Studies of migrants are very important for determination of host and environmental factors. Over much of the latest three decades, ASIRs for colon cancer among US-Japanese were almost the same as those among US-Whites. PRs of type II diabetes and IGT among US-Japanese were also higher than those among J-Japanese, and were the highest in three populations. Several reports have shown ASIRs for colon cancer and PRs for type II diabetes to be higher among US-Japanese Issei (first-generation) than among J-Japanese, and higher among US-Japanese Nisei than among US-Whites (Tokudome, 1996; King and Rewers, 1993). Dietary analysis has reported that US-Japanese Nisei men with diabetes consumed significantly greater amount of animal fat and animal protein than normal men, but energy intake was similar (Fujimoto et al., 1989). The same was the case for Brazilian-Japanese (Tsugane et al., 1989). Recently, ASIRs for colon cancer among US-Japanese were higher than those among US-Whites (27.7 and 26.1, and 21.8 and 19.7 per 100,000 population among US-Japanese and US-Whites men and the corresponding women in Los Angeles (1993-97), in that order (Parkin et al., 2002).

In 1975-93, PRs for type II diabetes and IGT adjusted for the world standard population were reported to be 10.1% and 17.3% among J-Japanese men aged 40-74y, and 6.0% and 15.8% among their female counterparts (Broder, 1993). Those rates among US-Whites aged 40-74y were reported to be 11.4% and 15.6% in 1976-80, and 14.3% and 15.6% in 1988-94, respectively (Harris et al., 1998). PRs for type II diabetes among J-Japanese men and women are moderate compared to levels in other population of the world, whereas PRs for IGT have been ranked moderate for men and high-moderate for women (Broder, 1993). Sasaki et al (1998) have reported that PRs for diabetes and IGT among US-Whites were almost same levels, but PRs for IGT among J-Japanese and US-Japanese were about 1.5 times higher than PRs for diabetes. We speculate that this reason may be not only changes in lifestyle factors such as dietary habits, but also interactions with Japanese inherent genetic predispositions with regard to the system for regulation of circulating glucose or abilities of metabolizing enzymes acting on meat and fat/oil may be operating.

Association between Colon Cancer and Diabetes

On this correlation analysis, we demonstrated that PRs for type II diabetes had a positive association with ASIRs for colon cancer among the combination of Japanese and US-Japanese. In three case-control studies among J-Japanese men, type II diabetes has demonstrated positive associations with colon adenomas (Kono et al., 1998; Nishi et al., 2001; Marugame et al., 2002). The prevalence and history of

diabetes as the risk factor of colorectal cancer have been documented in a number of case-control and large-scale cohort studies (La Vecchia et al., 1991; 1997; Hardell et al., 1995; Le Marchand et al., 1997; Will et al., 1998; Hu et al., 1999; Nilsen and Vatten, 2001; Levi et al., 2002). Type II diabetes and plasma insulin level have demonstrated positive associations with colorectal cancer in two reports as follows: 1) a long-term and large-scale cohort study for diabetes patients at baseline (Weiderpass et al., 1997), and 2) a study for persons aged 65y and older at baseline except for coronary heat diseases at elderly age (Schoen et al., 1999). From a Nurses' Health Study, the group of Hu firmly concluded that women had diabetes first, and later developed colon cancer (Volkers, 2000).

In four out of five reports, IGT, insulin resistance and plasma levels of glucose or insulin have demonstrated positive associations with the incidence and the death for colorectal cancer (Smith et al., 1992; Colangelo et al., 2002; Trevisan et al., 2001; Nilsen and Vatten, 2001; Schoen et al., 1999). Insulin is one of important growth factors for colonic epithelial cells, and McKeown-Eyssen (1994) and Giovannucci (1995) have suggested that lifestyle factors first lead to insulin resistance and this promotes the development of colon cancer. Many studies have suggested insulin-like growth factor (IGF)-I, IGF binding protein-3, the ratio of IGF-I/IGF binding protein-3 and C-peptide as biomarkers for colorectal cancer through insulin resistance (Ma et al., 1999; Kaaks et al., 2000; Shandhu et al., 2002). Those were involved in somatic growth, cell proliferation, transformation and p53-dependent apoptosis, IGF-I bioavailability and pancreatic insulin secretion, respectively.

Conclusions

Increment in ASIRs for colon cancer among J-Japanese might be closely associated with the increment in PRs for type II diabetes linked to changes in food intake toward the westernization of the diet. Our study demonstrated a positive association between PRs for type II diabetes and ASIRs for colon cancer among the combination of J-Japanese and US-Japanese. Compared with US-Whites, we speculate that J-Japanese and US-Japanese may have low resistance against both colon cancer and type II diabetes due to their responses to common risk factors such as meat and oil/fat. In future research, we should encourage evaluation of colon cancer in association with PRs for type II diabetes and make good use of the findings for primary prevention by lifestyle modification.

Acknowledgments

References

Broder S (1993). Perspectives on cancer in Japan and the United States. *Jpn J Cancer Res*, **84**, 821-30.

Bruce WR, Wolever TMS, Giacca A (2000). Mechanisms linking diet and colorectal caner: The possible role of insulin resistance. *Nutr Cancer*, **37**, 19-26.

Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K (2002). Colorectal cancer mortality and factors related to the insulin resistance syndrome. *Cancer Epidemiol Biomark Prev*, **11**, 385-91.

Fujimoto WY (1992). The growing prevalence of non-insulin-dependent diabetes in migrant Asian populations and its implications for Asia. *Diabetes Res Clin Pract*, **15**, 167-83.

Fujimoto WY, Bergstrom RW, Boyko EJ, et al (1994). Diabetes and diabetes risk factors in second- and third-generation Japanese Americans in Seattle, Washington. *Diabetes Res Clin Pract*, **24 (Suppl)**, 43-52.

Fujimoto WY, Bergstrom RW, Newell-Morris L, Leonetti DL (1989). Nature and nurture in the etiology of type 2 diabetes mellitus in Japanese Americans. *Diabetes Metab Rev*, **5**, 607-25.

Giovannucci E (1995). Insulin and colon cancer. *Cancer Causes Control*, **6**, 164-79.

Giovannucci E (2001). Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr*, **131 (Suppl)**, 3109-29.

Hara H, Egusa G, Yamakido M Kawate R (1994). The high prevalence of diabetes mellitus and hyperinsulinemia among the Japanese-Americans living in Hawaii and Los Angeles. *Diabetes Res Clin Pract*, **24 (Suppl)**, S37-42.

Hardell L, Fredrikson M, Axelson O (1995). Case-control study on colon cancer regarding previous diseases and drug intake. *Int J Oncol*, **8**, 439-44.

Harris MI, Flegal KM, Cowie CC, et al (1998). Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*, **21**, 518-24.

Hu FB, Manson JE, Liu S, et al (1999). Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst*, **91**, 542-7.

Islam MM, Horibe H, Kobayashi F (1999). Current trend in prevalence of diabetes mellitus in Japan, 1964-1992. *J Epidemiol*, **9**, 155-62.

Kaaks R, Toniolo P, Akhmedkhanov A, et al (2000). Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst*, **92**, 1592-600.

King H, Aubert RE, Herman WH (1998). Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*, **21**, 1414-31.

King H, Rewers M (1993). Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. WHO Ad Hoc Diabetes Reporting Group. *Diabetes Care*, **16**, 157-77.

Kono S, Honjo S, Todoroki I, et al (1998). Glucose intorelance and adenomas of the sigmoid colon in Japanese men (Japan). *Cancer Causes Control*, **9**, 441-6.

Kuroishi T, Hirose K, Tajima K, Tominaga S (1997). Cancer mortality in Japan (1950-1995). *Gann Monogr Cancer Res*, **47**, 1-82.

Kuzuya T (1994). Prevalence of diabetes mellitus in Japan compiled from literature. *Diabetes Res Clin Pract*, **24 (Suppl)**, 15-21.

La Vecchia C, D'Avanzo B, Negri E, Franceschi S (1991). History of selected diseases and the risk of colorectal cancer. *Eur J Cancer*, **27**, 582-6.

La Vecchia C, Negri E, Decarli A, Franceschi S (1997). Diabetes mellitus and the risk of primary liver cancer. *Int J Cancer*, **73**, 204-7.

Le Marchand L, Wilkens LR, Kolonel LN, Hankin JH, Lyu LC (1997). Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res*, **57**, 4787-94.

Levi F, Pasche C, Lucchini F, La Vecchia C (2002). Diabetes mellitus, family history, and colorectal cancer. *J Epidemiol Community Health*, **56**, 479-80.

Ma J, Pollak MN, Giovannucci E, et al (1999). Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst*, **91**, 620-5.

Marugame T, Lee K, Eguchi H, et al (2002). Relation of impaired glucose tolerance and diabetes mellitus to colorectal adenomas in Japan. *Cancer Causes Control*, **13**, 917-21.

McKeown-Eyssen G (1994). Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomark Prev*, **3**, 687-95.

Ministry of Health and Welfare of Japan, Health and Welfare Statistics and Information Department (1995; 2002), Journal of Health and Welfare Statistics, 42; 49. Tokyo: Health and Welfare Statistics Association. (in Japanese)

Ministry of Health and Welfare of Japan, Statistics and Information Department Minister's Secretariat (1974; 1982; 1992), Patients survey 1972; 1980; 1990. Tokyo: Health and Welfare Statistics Association. (in Japanese)

Ministry of Health, Labor and Welfare, Division of Health and Nutrition (1999; 2002), Kokumin-Eiyo-no-Genjo (Current Status of National Nutrition) 1997; 2000, Tokyo: Dai-ichi Shuppann. (in Japanese)

Mori M, Saitoh S, Takagi S, et al (2000). A review of cohort studies on the association between history of diabetes mellitus and occurrence of cancer. *Asian Pac J Cancer Prev*, **1**, 269-76.

Muir C, Waterhouse J, Mack T, Powell J, Whelan S (1987). Cancer Incidence in Five Continents V. No.88. Lyon: IARC.

Nilsen TIL, Vatten LJ (2001). Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Brit J Cancer*, **84**, 417-22.

Nishii T, Kono S, Abe H, et al (2001). Glucose intolerance, plasma insulin levels, and colorectal adenomas in Japanese men. *Jpn J Cancer Res*, **92**, 836-40.

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, Raymond L, Young J (1997). Cancer Incidence in Five Continents VII. No.143. Lyon: IARC.

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

Sasaki A, Tominaga M, Eguchi H, et al (1998). Comparison of the prevalence of diabetes mellitus and impaired glucose tolerance in Japan and other countries. *J Jpn Diab Soc*, **41**, 355-62. (in Japanese)

Schoen RE, Tangen CM, Kuller LH, et al (1999). Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst*, **91**, 1147-54.

Shandhu MS, Dunger DB, Giovannucci EL (2002). Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. *J Natl Cancer Inst*, **94**, 972-80.

Smith GD, Egger M, Shipley MJ, Marmot MG (1992). Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol*, **136**, 1110-4.

Tajima K, Hirose K, Nakagawa N, Kuroishi T, Tominaga S (1985). 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 (1985). Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya. *Jpn J Cancer Res* (Gann), **76**, 705-16.

Terao A, Konishi M, Baba S, Mannami T (1997). Prevalence of glucose intolerance, diabetes mellitus, and high serum insulin levels in a Japanese urban population. *Nippon Koshu Eisei Zasshi*, **44**, 283-91. (in Japanese)

Tokudome S (1996). Frequency and distribution of cancer and interaction between host and environmental factors. *Gann Monogr Cancer Res*, **44**, 21-8.

Tominaga S, Kuroishi T (1997). An ecological study on diet/nutrition and cancer in Japan. *Int J Cancer*, 10 (Suppl), 2-6.

Trevisan M, Liu J, Muti P, et al (2001). Markers of insulin resistance and colorectal cancer mortality. *Cancer Epidemiol Biomark Prev*, **10**, 937-41.

Tsugane S, Gotlieb SL, Laurenti R, Souza JM, Watanabe S (1989). Mortality and cause of death among first-generation Japanese in Sao Paulo, Brazil. *Int J Epidemiol*, **18**, 647-51.

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.

Volkers N (2000). Diabetes and Cancer: Scientists search for a possible link. *J Natl Cancer Inst*, **92**, 192-4.

Weiderpass E, Gridley G, Nyren O, et al (1997). Diabetes mellitus and risk of large bowel cancer. *J Natl Cancer Inst*, **89**, 660-1.

Will JC, Galuska DA, Vinicor F, Calle EE (1998). Colorectal cancer: Another complication of diabetes mellitus? *Am J Epidemiol*, **147**, 816-25.