Table 2. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of colorectal adenomas with smoking and drinking by size[1]

Variable	Colorectum		Proximal colon		Distal colon		Rectum	
	Small[2] (n=442)	Large[2] (n=285)	Small[2] (n=165)	Large[2] (n=84)	Small[2] (n=181)	Large[2] (n=98)	Small[2] (n=40)	Large[2] (n=37)
Cigarette-years[3]								
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1–399	1.0 (0.7–1.3)	1.7 (1.1–2.7)	0.9 (0.5–1.5)	1.4 (0.7–2.9)	1.0 (0.6–1.6)	1.0 (0.5–2.0)	0.9 (0.3–3.1)	5.1 (1.6–16.2)
400–799	1.6 (1.2–2.1)	2.5 (1.7–3.6)	1.4 (0.9–2.2)	2.2 (1.2–4.0)	1.7 (1.1–2.5)	1.6 (0.9–2.8)	2.3 (0.9–5.5)	2.1 (0.6–6.9)
≥800	2.0 (1.4–2.9)	3.4 (2.2–5.3)	2.1 (1.3–3.5)	2.5 (1.2–5.1)	1.4 (0.8–2.4)	2.8 (1.5–5.2)	4.1 (1.5–11.1)	8.2 (2.5–26.8)
Trend	P=0.0001	P=0.0001	P=0.002	P=0.004	P=0.017	P=0.001	P=0.0024	P=0.007
Alcohol (ml/d)								
Never	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
<30[4]	1.1 (0.8–1.7)	0.9 (0.6–1.4)	1.1 (0.6–1.8)	0.7 (0.4–1.6)	0.9 (0.5–1.6)	0.7 (0.3–1.5)	3.9 (0.9–17.7)	1.0 (0.3–3.4)
30–59[4]	1.7 (1.2–2.5)	1.4 (0.9–2.2)	1.3 (0.7–2.2)	1.0 (0.5–2.0)	1.7 (1.0–2.9)	1.6 (0.8–3.0)	4.8 (1.1–21.6)	1.2 (0.4–4.1)
≥60[4]	1.5 (1.1–2.2)	1.7 (1.1–2.5)	1.3 (0.8–2.2)	1.3 (0.6–2.5)	1.4 (0.8–2.4)	1.5 (0.8–3.0)	2.9 (0.6–13.5)	1.9 (0.6–6.0)
Trend	P=0.004	P=0.0007	P=0.26	P=0.25	P=0.024	P=0.027	P=0.39	P=0.13

1) Adjusted for rank, hospital, body mass index, physical activity, and either alcohol intake or smoking. Adenoma cases of unknown size and past drinkers were excluded.
2) Small and large adenomas were defined as those of <5 mm and ≥5mm in diameter, respectively.
3) Cigarettes smoked per day multiplied by years of smoking.
4) Amount of ethanol (ml) consumed per day in current drinkers.

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of colorectal adenomas with smoking and drinking by multiplicity[1]

Variable	Colorectum		Proximal colon		Distal colon		Rectum	
	Single (n=331)	Multiple (n=399)	Single (n=178)	Multiple (n=71)	Single (n=199)	Multiple (n=83)	Single (n=61)	Multiple (n=17)
Cigarette-years[2]								
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1–399	1.0 (0.7–1.4)	1.5 (1.0–2.3)	1.0 (0.6–1.6)	1.2 (0.5–2.9)	0.9 (0.5–1.4)	1.3 (0.6–3.1)	2.2 (0.9–5.0)	3.3 (0.3–36.9)
400–799	1.2 (0.9–1.6)	3.1 (2.2–4.2)	1.4 (0.9–2.1)	2.5 (1.3–4.9)	1.4 (1.0–2.1)	2.7 (1.4–5.3)	1.6 (0.7–3.5)	9.5 (1.2–75.1)
≥800	1.7 (1.2–2.4)	3.6 (2.4–5.3)	2.1 (1.3–3.4)	2.7 (1.2–6.0)	1.4 (0.9–2.4)	3.4 (1.6–7.3)	5.2 (2.3–11.7)	9.9 (1.1–91.9)
Trend	P=0.015	P=0.0001	P=0.002	P=0.003	P=0.029	P=0.0002	P=0.0009	P=0.001
Alcohol (ml/d)								
Never	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
<30[3]	1.0 (0.6–1.4)	1.1 (0.7–1.7)	1.0 (0.6–1.6)	0.9 (0.4–2.1)	1.0 (0.6–1.7)	0.4 (0.1–1.0)	1.6 (0.6–4.5)	3.8 (0.4–32.1)
30–59[3]	1.2 (0.9–1.6)	1.9 (1.3–2.9)	1.0 (0.6–1.7)	1.5 (0.7–3.3)	1.6 (1.0–2.7)	1.8 (0.9–3.7)	2.2 (0.8–6.1)	3.7 (0.4–31.8)
≥60[3]	1.7 (1.2–2.4)	1.9 (1.3–2.8)	1.1 (0.7–1.9)	1.7 (0.8–3.8)	1.4 (0.8–2.3)	1.7 (0.8–3.5)	2.3 (0.8–6.2)	2.4 (0.3–22.0)
Trend	P=0.042	P=0.0001	P=0.53	P=0.048	P=0.06	P=0.003	P=0.08	P=0.72

1) Adjusted for rank, hospital, body mass index, physical activity, and either alcohol intake or smoking. Past drinkers were excluded.
2) Cigarettes smoked per day multiplied by years of smoking.
3) Amount of ethanol (ml) consumed per day in current drinkers.

Table 4. Adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of colorectal adenomas stratified by cigarette smoking according to alcohol use[1]

Cigarette-years[2]	Alcohol (ml/day)						Trend
	0–29		30–59		≥60		
	No.[3]	OR (95% CI)	No.[3]	OR (95% CI)	No.[3]	OR (95% CI)	
0	68/271	1.0 (referent)	41/120	1.3 (0.8–2.1)	39/93	1.7 (1.1–2.7)	P=0.02
1–399	39/128	1.0 (referent)	38/98	1.3 (0.8–2.3)	39/75	1.7 (1.0–2.9)	P=0.06
≥400	140/289	1.0 (referent)	161/191	1.8 (1.3–2.4)	165/229	1.5 (1.1–2.0)	P=0.006

1) Adjusted for hospital, rank, body mass index, and physical activity. Past drinkers were excluded.
2) Number of cigarettes smoked per day multiplied by years of smoking.
3) Numbers of cases/controls.

tion with multiple adenomas was noted for each site of adenomas. The association between alcohol and adenomas did not differ much by either size or multiplicity of adenomas, whether the analysis was done for colorectal adenomas as a whole or site-specific adenomas.

Table 4 shows the relation between alcohol use and colorectal adenomas stratified by cigarette smoking. The ORs of colorectal adenomas increased progressively with increasing levels of alcohol consumption among lifelong non-smokers and light smokers (<400 cigarette-years). There was no stepwise increase in the OR with increasing consumption of alcohol among those with high exposure to smoking, but the trend was highly significant. The increasing trend of the association between alcohol and colorectal adenomas did not statistically significantly differ by smoking habit.

Discussion

Cigarette smoking was strongly associated with increased risks of adenomas of each of the proximal colon, distal colon, and rectum. The increase in the OR of rectal adenomas associated with smoking was seemingly substantial. However, the number of cases with rectal adenomas was relatively small, and further studies are needed to confirm the present finding regarding smoking and rectal adenomas. Such a differential association of smoking with rectal adenomas has not been observed previously. In the data of the earlier SDF study based on sigmoidoscopy,[23] smoking was not more strongly associated with rectal adenomas than with sigmoid colon adenomas. Elsewhere, three studies have examined the relation of smoking to colorectal adenomas by location of adenomas,[17,18,22] In a case-control study in the United States,[17] smoking was associated with a more than 3-fold increased risk of proximal colon adenomas and a 2-fold increased risk of adenomas of the distal colon and rectum combined in men. A prospective study in Japan reported a statistically significant 2.5-fold increase in the risk of proximal colon adenomas among men smoking more than 20 pack-years and a less evident, statistically nonsignificant increase in the risk of each of distal colon and rectal adenomas.[18] In these studies, however, it is uncertain how completely the colon was investigated. Subjects undergoing colonoscopy beyond the splenic flexure were included in the former study,[17] and details were not described regarding the depth of intubation of colonoscopy among cases in the latter study.[18] While the ratio of cases with proximal colon adenomas to those with distal colon adenomas was 0.88 in the present study, the corresponding ratios in the former[17] and the latter study[18] were 0.78 and 0.66, respectively. If colonoscopy was more extensively performed in smokers, a stronger, positive association with smoking would spuriously emerge for proximal colon adenomas. On the other hand, a case-control study in Japan showed a null association with smoking for proximal colon, distal colon, and rectal adenomas.[22] In that study, controls were community residents who probably had not undergone colonoscopy, and thus the association between smoking and adenomas was necessarily underestimated.

Several case-control studies have addressed the relation of smoking to site-specific colorectal cancer.[25-31] Smoking was related to an increased risk of rectal cancer, but not of either proximal or distal colon cancer in Japan[26] and China.[25] A population-based case-control study in the United States reported that smoking was significantly associated with a modest increase in the risk of each of proximal and distal colon cancer, regardless of sex.[28] In a population-based case-control study in Hawaii,[29] tobacco smoking was associated with a statistically significantly increased risk of distal colon cancer in men, and a non-significantly increased risk of proximal colon cancer in women; a modest, statistically non-significant increase in the risk of rectal cancer in association with smoking was noted in both men and women. Contrary to these findings, smoking was not related to increased risk of either proximal colon or distal colon or rectal cancer in other studies.[30,31] Two points should be noted in interpreting the results from studies on smoking and colorectal cancer. Part of the controls included those with colorectal adenomas, because they did not undergo colonoscopy. Not all cases of colorectal cancer are derived from adenomas. If the proportion of adenoma-related cancer cases is smaller, the association between smoking and colorectal cancer is necessarily weaker.[32]

In the present study, alcohol drinking was related to increased risks of distal colon and rectal adenomas, but not materially associated with proximal colon adenomas. The findings are consistent with the previous observation in the SDF study that alcohol use was weakly related to both sigmoid colon adenomas and rectal adenomas.[23] To our knowledge, only two studies have previously examined the association between alcohol drinking and risk of colorectal adenomas by subsite. One study reported that daily alcohol drinking was associated with increased risks of proximal and distal colon adenomas, but not of rectal adenomas.[22] The other study showed an increased risk of rectal adenomas associated with a consumption of more than 30.3 g of ethanol per day, but the relation between alcohol and adenomas at other sites was not referred to.[18] A meta-analysis combining 5 cohort studies and 22 case-control studies reported a 10% excess risk of colorectal cancer associated with a consumption of 24 g of alcohol per day, and there was no difference in the excess risk between colon and rectal cancer.[6]

Cigarette smoking, not alcohol use, tended to be more strongly associated with large adenoma (≥5 mm) and with multiple adenomas regardless of the location of adenomas in the present study. Several studies have previously examined the relation between smoking and colorectal adenomas according to the size of adenomas, by defining adenoma ≥10 mm as large adenoma.[17,24,33,34] In these studies, smoking was generally related to increased risks of both small and large adenomas with almost the same magnitude of the increased risks. On the other hand, in the early study of sigmoid colon adenomas in SDF men,[16] smoking was related to a slightly greater increase in the risk of small adenomas (<5 mm) than of large adenomas (≥5 mm). However, the number of adenoma cases was rather small; cases of small (<5 mm) and large (≥5 mm) adenomas numbered only 86 and 72, respectively. Two studies have examined the relation of smoking to single and multiple colorectal adenomas separately.[17,22] One study suggested a stronger association of smoking with multiple adenomas,[17] but the other found no association with either single or multiple adenomas.[22] With respect to alcohol intake, a stronger, positive association was observed for large colorectal adenomas (≥10 mm) in one study,[24] but not in another study.[10] In the above-mentioned small study of the SDF men,[16] alcohol use was related to a greater increase in the risk of large adenomas (≥5 mm) of the sigmoid colon than of small adenomas. Alcohol use was shown to be associated with an increased risk of multiple, but not single, colorectal adenomas in a case-control study in Japan.[22] Previous studies regarding the relation of smoking or alcohol use to colorectal adenomas by adenoma size and multiplicity generally suffered from the small number of adenoma cases, and the present findings need to be corroborated in further studies.

Several studies suggest that smoking may exert an initiating effect and alcohol may promote colorectal carcinogenesis.[16,24,26] Thus, it was expected that the relation to alcohol consumption would be stronger in smokers than in nonsmokers. However, there was no measurable effect modification by smoking status in the relation between alcohol and colorectal adenomas. The present findings are in agreement with the observations in previous studies examining the interaction between smoking and alcohol in the occurrence of colorectal adenomas[9,12,26] and cancer.[27]

This study had several methodological advantages. More than 95% of the subjects received colonoscopy, and the analysis was based on the subjects undergoing total colonoscopy. Thus, selection bias and misclassification as regards outcome were reduced substantially. Lifestyle factors were ascertained prior to colonoscopy, and thus recall bias regarding smoking and alcohol use could be excluded. Further, the subjects were relatively homogeneous regarding age, ethnicity, and occupation, and confounding is unlikely to explain the present findings.

It is a limitation of the present study that dietary factors such as vegetables, meat, and fat were not taken into account. These dietary factors are considered to play an important role in colorectal carcinogenesis.[3,4] However, it is unlikely that the ob-

served associations of smoking and alcohol use with colorectal adenomas were totally confounded by dietary factors. An increased risk of colorectal adenomas associated with smoking or alcohol use has been observed with adjustment for dietary factors, which were related to colorectal cancer or adenomas, in many studies.[5,6,11,33,34] The interaction of smoking and alcohol use with dietary factors may also be important in colorectal carcinogenesis. For instance, the association between alcohol and colorectal adenomas may be modified by folate intake. Alcohol is an antagonist of folate, which may be protective against colorectal cancer.[35] It was shown that an increased risk of colorectal cancer associated with alcohol use was attenuated with high folate intake.[36] Another limitation was that only current alcohol consumption was ascertained; the current intake may not be relevant to the occurrence of colorectal adenomas, although former alcohol use was distinguished from lifelong abstinence. Furthermore, male officials in the SDF are not representative of middle-aged Japanese, and it may be difficult to generalize the present findings.

In conclusion, the present study demonstrated that cigarette smoking was associated with an increased risk of adenomas at each of the proximal colon, distal colon, and rectum. Alcohol use was associated with moderately increased risks of distal colon and rectal adenomas, but not of proximal colon adenomas. Cigarette smoking, not alcohol drinking, was associated with greater increases in the risk of large adenomas and of multiple adenomas across the colorectum. There was no indication of an interaction between smoking and alcohol use in the risk of colorectal adenomas.

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Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan

S Kono

Mortality from colon cancer has rapidly increased in the past decades in Japan, and the increase has generally been ascribed to the Westernized diet, characterized by a high intake of fat and meat. However, fat and meat consumption in Japan stopped increasing in the 1970s. The secular trend of colon cancer incidence and mortality was examined in relation to changing patterns of the consumption of selected foods and nutrients and other related factors in Japan, focusing on the relationship with fat and meat consumption. The incidence and mortality rates of colon cancer both increased almost linearly on a log scale until the early 1990s, the increase then ceasing. The temporal change in fat and meat intake coincided with the incidence of colon cancer approximately 20 years later. Although figures for the consumption of red meat was not available in the early years, red meat accounted for 70–80% of the total meat intake in the mid 1960s and thereafter. Cereal consumption showed a continuous decrease even after the 1970s, that of vegetables showing no marked change. The current observation adds to evidence that red meat intake is an important determinant of colon cancer risk. *European Journal of Cancer Prevention* **13:127–132 © 2004 Lippincott Williams & Wilkins.**

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Key words: Colon cancer, fat, meat, secular trend

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Introduction

A high-fat diet has generally been implicated in the aetiology of colorectal cancer (Boyle and Langman, 2000), but recent observational studies of individuals have suggested that the intake of meat, especially red meat, rather than of fat is associated with an increased risk of colon or colorectal cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997). Mortality from colon cancer has rapidly increased in the past few decades in Japan, and the increase has generally been ascribed to the Westernized diet, characterized by a high intake of fat and meat (Kono, 1996). However, fat and meat consumption in Japan stopped increasing in the 1970s (Kono, 1996; Kono and Ahn, 2000). On the other hand, vegetable consumption is regarded as protecting against colon or colorectal cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997). Epidemiological findings are inconsistent regarding protective associations with cereals, calcium, carotenoids and vitamin C (World Cancer Research Fund and American Institute for Cancer Research, 1997). Fish and soy foods have also attracted interest as foods that may confer a reduced risk of colorectal cancer (Caygill and Hill, 1995; Messina and Bennink, 1998). This paper examines the secular trend of colon cancer incidence and mortality in relation to the changing patterns of consumption of selected foods and nutrients, and other related factors in Japan, focusing on the relationship with fat and meat consumption.

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Materials and methods

Annual per capita consumptions of selected nutrients and foods were derived from a series of publications from the National Nutrition Survey during the period from 1950 to 2000 (Japan Ministry of Health, Welfare and Labour, 2002a). This nationwide survey started in 1948, and per capita consumptions of foods and nutrients have been reported based on annual surveys of households selected randomly across the nation. Until 1993, the survey used the method of weighing the foods consumed in each household over 3 days; since 1994, it has used consumption in 1 day. The food group of meat included poultry, and fish included shellfish. The consumptions of individual types of meat were not separately recorded in the early years, and the consumption of red meat (beef, pork, and ham and sausage combined) was calculated for each year from 1966 to 2000. Tofu for the period 1950–1963 included a small amount of soybean products other than tofu and miso (fermented soybean paste). The intake of carotene and retinol combined was recorded as an intake of vitamin A. The means of height and body weight for different age groups have also been reported in men and women separately in the National Nutrition Survey. Body mass index (kg/m^2) was estimated from these reported mean heights and weights. Alcohol intake per adult was estimated from the taxed sales of four alcoholic beverages (*sake*, *shochu*, beer and whiskey/brandy) in each of the fiscal years since 1951 (National Tax Administration Agency, 2002). Missing data for tofu

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and miso in the years 1964 and 1965, and for body mass index in the year 1974, were estimated by interpolation.

Annual age-adjusted incidence rates of colon cancer were available for the period 1975–1997; the incidence rates were estimated on the basis of data from 12 cancer registries across the nation (Research Group for Population-based Cancer Registration in Japan, 2002). Age-adjusted mortality rates of colon cancer between 1950 and 2000 were also obtained from published reports (Tominaga and Oshima, 1999; Japan Ministry of Health, Welfare and Labour, 2002b). Age adjustment in incidence and mortality was achieved by the direct method, with the 1985 model population in Japan as the standard population.

Pearson's correlation coefficients of annual data on consumption and body mass index with colon cancer rates were calculated with a lag time of 20 years, i.e. the consumption data and body mass index of 20 years earlier were correlated to the current set of colon cancer rates. The correlation coefficients were also calculated allowing for a lag time of 10 or 30 years, but the correlations with fat and meat were weaker than with those based on the lag time of 20 years.

Results

Of the variables under study, fat, meat, alcohol and body mass index were highly, positively correlated with colon cancer incidence and mortality. Cereal and miso consumption showed strong, negative correlations with colon cancer rates (Table 1). The other variables also showed fairly large correlation coefficients in general.

Changes in food and nutrient consumption and the trend of colon cancer were depicted to examine the temporal relationship in detail. Meat intake markedly increased from 1950 until the early 1970s, and thereafter the intake was almost constant in the range 70–80 g/day (Fig. 1). The secular trend of red meat intake almost paralleled that of total meat intake. Red meat accounted for approximately 70% of meat intake during the period 1966–1971, 80% in the years 1972 and 1973, and 75% thereafter. There was a small peak in red meat intake as well as total meat intake in the early 1970s. This peak was attributable to a more than doubling in the consumption of ham and sausage in 1972 and 1973 compared with the preceding year. Fat intake also increased until the mid-1970s, but the rate of increase was less marked than that observed for meat intake. Fat intake lay in the range 55–60 g/day during the period 1975–2000.

Both the incidence and the mortality rate of colon cancer increased almost linearly in logarithmic fashion until early 1990s, the increase being more marked for incidence than for mortality (Fig. 1). The incidence of colon cancer ceased to increase in early 1990s, whereas the end of the increase in mortality from colon cancer was delayed for several years. Temporal changes in the consumption of foods and nutrients other than fat and meat are shown in Fig. 2. Cereal consumption decreased continuously even after the 1970s, and vegetables and fish showed a gradual, small increase in consumption. Of the two common soy foods, tofu showed a trend towards higher consumption, whereas miso consumption decreased steadily. Calcium and vitamin C consumption increased slightly in the earlier years and were constant after the mid-1960s and 1970s. Alcohol intake showed a fairly rapid increase in the 1950s and 1960s, the increase being modest thereafter; the average daily intakes per adult in 1951, 1961, 1971 and 1981 were 5.1 g, 10.7 g, 15.1 g and 17.6 g respectively (data not depicted).

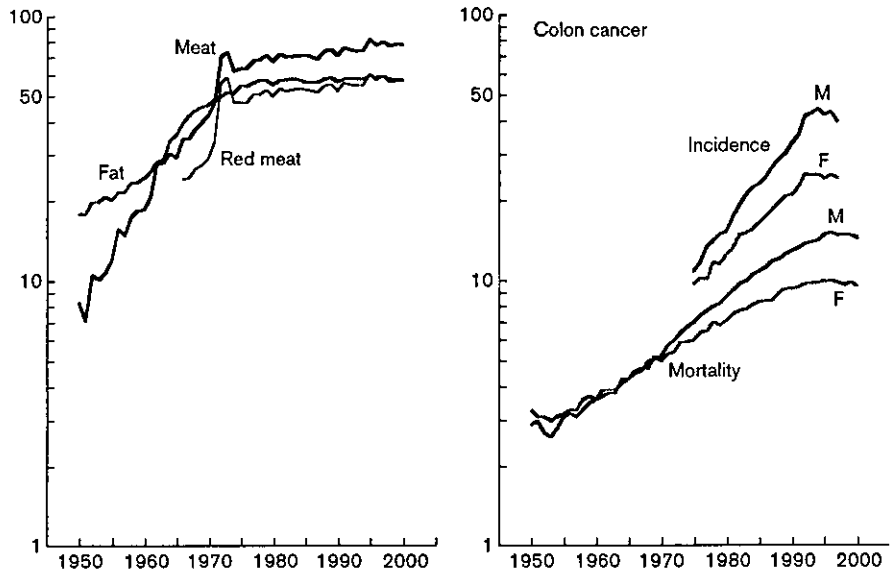
The body mass index of men increased progressively over time regardless of age group. Women's body mass index also increased until the early 1970s but did not show an

Table 1 Pearson's correlation coefficients of selected dietary variables and body mass index (BMI) with annual incidence and mortality rates of colon cancer (per 100 000) with a lag time of 20 years

Variable (unit)	Incidence ($n=23$)[a]		Mortality ($n=31$)[b]	
	Male	Female	Male	Female
Energy (kcal/day)	0.78	0.81	0.73	0.75
Fat (g/day)	0.97	0.98	0.99	0.96
Calcium (mg/day)	0.93	0.95	0.96	0.97
Vitamin A (IU/day)[c]	0.90	0.89	0.90	0.86
Vitamin C (mg/day)	0.87	0.86	0.80	0.74
Cereals (g/day)	−0.97	−0.98	−0.98	−0.96
Vegetables (g/day)	0.77	0.75	0.70	0.66
Meat (g/day)	0.98	0.97	0.96	0.93
Fish (g/day)	0.93	0.93	0.87	0.85
Tofu (g/day)	0.59	0.62	0.80	0.83
Miso (g/day)	−0.95	−0.94	−0.95	−0.92
Alcohol (g/day)	0.96	0.98	0.99	0.99
BMI (kg/m^2) at age 30s	0.98	0.80	0.95	0.61
BMI (kg/m^2) at age 40s	0.96	0.98	0.94	0.94

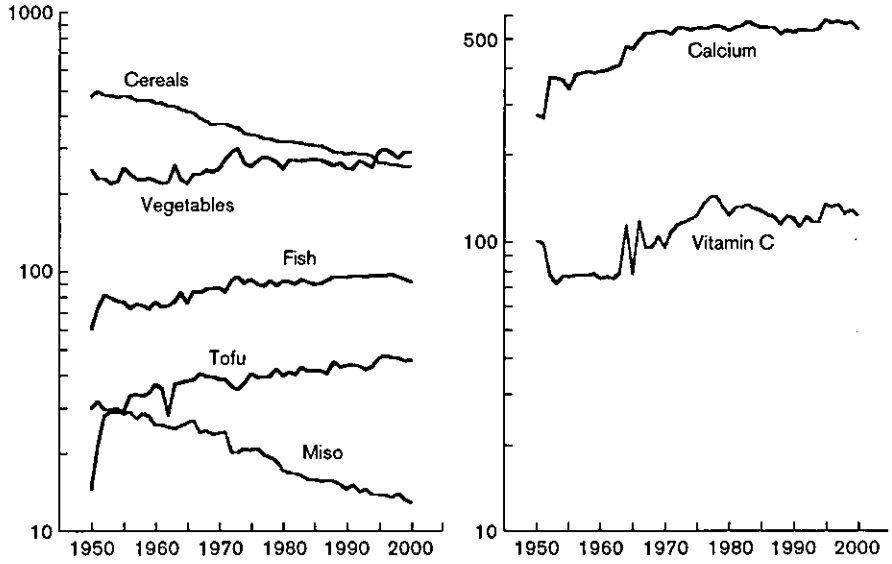
[a]Annual consumptions and BMI in the period 1955–1977 were correlated to annual incidence rates in the period 1975–1997.
[b]Annual consumptions and BMI in the period 1950–1980 were correlated to annual mortality rates in the period 1970–2000.
[c]Data were not available for the period 1950–1954.

Fig. 1



Left: Annual per capita consumptions (g/day) of fat and meat in Japan, 1950–2000. *Right*: Age-adjusted annual incidence and mortality rates of colon cancer (per 100 000) for males and females in Japan, 1950–2000. The standard population is the model population for 1985 in Japan.

Fig. 2



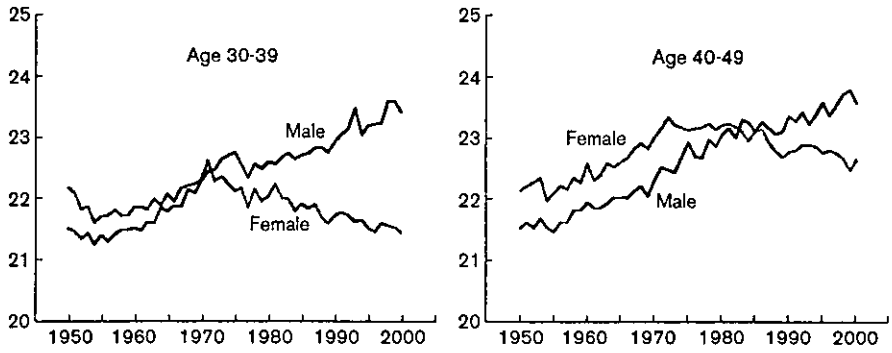
Annual per capita consumptions (g/day) of selected foods and nutrients in Japan, 1950–2000.

increasing trend thereafter. Younger women showed a decreasing trend of body mass index during the period from the 1970s to the 1990s (Fig. 3).

Discussion

Between-population studies are subject to the so-called ecological bias; i.e. an association observed on the level of populations does not necessarily represent the association on the individual level. Thus, an ecological correlation is generally ranked lowest in terms of strength of evidence for causality (Grimes and Schulz, 2002). The primary problem of ecological studies is that many potential determinants of disease other than the factors under study may vary between populations. The use of

Fig. 3

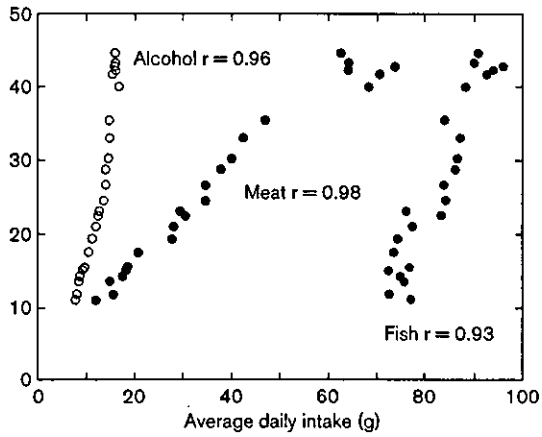


Body mass index (kg/m^2) of men and women aged 30–39 and 40–49 years calculated from the average height and body weight in Japan, 1950–2000.

aggregate data for populations is another problem. For example, gender difference is neglected in the average per capita consumption. Most of the alcohol is probably consumed by men in Japan, and the change in the per capita alcohol consumption may not be relevant to the trend of colon cancer in women. Nevertheless, consistency with ecological data strengthens a causal inference regarding a factor found to be associated with disease risk in case–control or cohort studies. If exposure to such a factor is an important determinant of disease, findings from observational studies of individuals should be related to the differences in disease risk over time within populations and between populations (Davey Smith and Ebrahim, 2003).

It should be noted that correlation coefficients are often misleading. Even a factor with a small variation, which may not be of biological relevance, can show a high correlation with disease rates. Colon cancer incidence and mortality showed high correlations with alcohol intake and fish consumption as well as with fat and meat. As illustrated in Fig. 4, however, the relationships of alcohol and fish with colon cancer were much less marked than that observed for meat intake. Graphical presentation is thus helpful in interpreting the values of correlation coefficients.

Fig. 4



Scattergrams of annual incidence rates of male colon cancer (per 100 000) for the years 1975–1997 in relation to annual per capita consumptions of alcohol, meat and fish (g/day) for the years 1955–1977, with a lag time of 20 years.

The temporal change in fat and meat intake coincided with the incidence of colon cancer approximately 20 years later. The increase in meat intake in the earlier years was more marked than that in fat intake, and it can be argued that the change in meat intake is primarily responsible for the increasing trend of colon cancer in Japan. Although the role of individual fatty acids in colon carcinogenesis cannot be denied (Sheppach *et al.*, 1997; Nkondjock *et al.*, 2003), many case–control and cohort studies have failed to find a positive association between total fat intake and colon cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997). On the other hand, several case–control and cohort studies have shown an increased risk of colon or colorectal cancer associated with a high intake of red or processed meat (World Cancer Research Fund and American Institute for Cancer Research, 1997; Norat *et al.*, 2002), although consensus has not been reached regarding the role of red meat in colon carcinogenesis (Hill, 2001). A recent cohort study failed to find an increased risk of colon cancer associated with meat as a whole or red meat (Flood *et al.*, 2003). The consumption of red meat was not recorded in the 1950s, but the temporal change in meat consumption is considered to have largely reflected the change in red meat consumption. Red meat contributed to the majority

of meat intake in the mid 1960s and thereafter. The temporary increase in the consumption of ham and sausage in early 1970s is surprising; the reason for this is unknown.

Japanese in the USA are among populations with the highest incidence rates of colon cancer in the world (Parkin *et al.*, 2002). In a survey conducted in Hawaii and California during the period 1993–1996 (Kolonel *et al.*, 2000), fat intake was 70 g/day in Japanese men and 60 g/day in Japanese women, whereas meat intake in Japanese men and women was 110 g/day and 80 g/day respectively. These data support the role of meat intake in colon carcinogenesis.

Although expert panels have agreed that vegetables are protective against colon cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997; WHO Consensus Panel, 1999), the pattern of vegetable consumption does not explain the increasing trend of colon cancer in Japan. The decreasing consumption of cereals was highly correlated with the increasing trend of colon cancer incidence and mortality, but the unvarying and continuous decrease of cereal intake did not correspond to the halt in the increase in colon cancer rates. Cereals are a major source of dietary fibre in the Japanese diet, and fibre intake also decreased continuously, as estimated elsewhere: 22.5 g/day in 1955, 17.4 g/day in 1975 and 15.6 g/day in 1991 (Munakata *et al.*, 1995). As regards calcium, vitamin C and tofu, which may be protective against colon cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997; Messina and Bennink, 1998), the consumption showed an upward, rather than downward, trend. Alcohol intake has been related to a modest increase in the risk of colon cancer in case–control and cohort studies, as reviewed elsewhere (Longnecker *et al.*, 1990). Alcohol consumption showed a fairly large increase in the early two decades and may explain part of the increase in colon cancer among men, although probably not in women. On the other hand, the changing pattern of body mass index may be regarded as compatible with the trend of colon cancer in women but not men.

Smoking, physical activity, hormone replacement therapy and use of aspirin were not considered in the present analysis because long-term relevant data were not available. Smoking was shown to be related to an increased risk of colon or colorectal cancer in several, but not all, epidemiological studies (Giovannucci, 2001). The prevalence of smoking in Japan has been reported since 1965; this has steadily declined from 80% in 1965 to 60% in 2000 in men, and has been constant at 15% during this period in women (Japan Tobacco Inc., 2002). Thus, smoking does not seem to explain the increasing trend of colon cancer in either men or women. Physical activity has consistently been related to a decreased risk of colon cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997). Physical activity may have declined, especially in men, as suggested by a trend towards higher levels of body mass index. Hormone replacement and aspirin use have also been shown to be protective against colon cancer in the USA and Europe (Beral *et al.*, 2002; Thun *et al.*, 2002), but the effects of these factors on the secular trend of colon cancer in Japan cannot be addressed. Interestingly, the mortality rates of colon cancer in men and women began to diverge in the early 1970s, and the male predominance in mortality and incidence has become more evident in recent years. This phenomenon is in agreement with observations reported elsewhere. It is noted that the incidence of colon cancer is higher in men than in women in high-incidence populations (DeCosse *et al.*, 1993). In migrants moving from a low-risk to a high-risk country, the incidence tended to increase more rapidly in men than in women (Ziegler *et al.*, 1986). Although smoking and alcohol consumption are probably not major determinants of the increasing trend of colon cancer in Japan, these two factors may modify colon carcinogenesis, resulting in a greater increase in the rate of colon cancer in men. Physical activity may have differed in men and women, as suggested by the different changing patterns of body mass index. A gender difference in food and nutrient consumption is also possible. Furthermore, reproductive and hormonal factors in women may explain the slow increase in incidence of colon cancer (DeCosse *et al.*, 1993).

Finally, it should be noted that the mortality and incidence of colon cancer seem to have declined in very recent years, especially among men. It is possible that early detection and improved treatment may result in a decline in colon cancer mortality and that the burgeoning practice of colorectal polypectomy may be related to the decline in colon cancer incidence. The phenomenon could also be a random variation in the annual rates of incidence and mortality, and monitoring the future trend is necessary to confirm the decreasing trend.

Conclusions

In Japan, fat and meat intake increased until early 1970s and has been constant for the past 25 years. Colon cancer incidence and mortality stopped increasing in the early 1990s, and this pattern in time trend coincides with the change in fat and meat intake observed 20 years earlier. The current observation adds to evidence that red meat intake is an important determinant of colon cancer risk.

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Circ J 2004; **68:** 405–409

Relation of Serum Total Cholesterol and Other Risk Factors to Risk of Coronary Events in Middle-Aged and Elderly Japanese Men With Hypercholesterolemia

—— The Kyushu Lipid Intervention Study ——

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Background The role of serum total cholesterol (TC) in the development of coronary heart disease (CHD) may differ in different age groups.

Methods and Results The relation of serum TC and other risk factors to CHD events was examined in middle-aged (<65 years) and elderly (≥65 years) men separately in the Kyushu Lipid Intervention Study (KLIS). Subjects were 4,349 men aged 45–74 years with serum TC of 220 mg/dl or greater who had no history of myocardial infarction, coronary angioplasty, or stroke. There were 123 CHD events (ie, myocardial infarction, coronary bypass surgery, coronary angioplasty, cardiac death, and sudden death) in a 5-year follow-up period. The Cox proportional hazards model was used with baseline and follow-up serum TC, baseline high-density lipoprotein (HDL) cholesterol, hypertension, diabetes mellitus, and other factors as covariates. Serum TC concentration during the follow-up, not at baseline, was associated with an increased risk of CHD events, especially in elderly men. High concentrations of serum HDL cholesterol were associated with a modest, statistically nonsignificant decrease in the risk among middle-aged men. An increased risk of CHD events associated with diabetes mellitus was greater in middle-aged men. Hypertension and smoking were not measurably related to the risk in either middle-aged or elderly men.

Conclusions Both the serum TC concentration during follow-up and diabetes mellitus are important predictors of CHD events in Japanese men with moderately elevated serum TC. (*Circ J* 2004; **68:** 405–409)

Key Words: Coronary heart disease; Diabetes mellitus; Japanese men; Serum total cholesterol

Elevated concentrations of serum total cholesterol (TC) or low-density lipoprotein (LDL) cholesterol are related to an increased risk of coronary heart disease (CHD), not only in Western populations[1] but also in Asian populations?[2–5] Further, primary and secondary prevention trials have demonstrated that lowering cholesterol results in a substantial decrease in the risk of CHD events[6–10] However, the value of lowering cholesterol in the elderly has been a matter of controversy. Several[11–13] but not all[4–16] prospective studies suggested a diminished or null association between serum TC and CHD risk in elderly persons. Recently in Europe, pravastatin use was shown to be beneficial in the prevention of CHD in those aged 70 years or older who had a history of, or risk factors for, vascular disease![17] Very few studies have addressed the relation of serum TC or LDL cholesterol and other risk factors to CHD in the elderly in Japan. A case–control study showed an increased risk of nonfatal myocardial infarction associated with hypercholesterolemia in middle-aged Japanese, but not in the elderly![4] In a small trial of elderly Japanese men and women![18] a high dose of pravastatin resulted in a greater decrease in the combined events of cardiovascular diseases including stroke, as compared with a low dose of pravastatin. In the study reported here, we examined the relation of serum TC and other risk factors to the risk of CHD events in middle-aged and elderly Japanese men separately, using the data compiled in the Kyushu Lipid Intervention Study (KLIS), a primary prevention trial of CHD events and cerebral infarction in Japanese men with moderately elevated concentrations of serum TC![19–21]

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Methods

Details of the study design and primary results of the KLIS have been described previously![19–21] In brief, a total of 5,640 men aged 45–74 years with serum TC of 220 mg/dl or greater were enrolled by 902 physicians in the Kyushu District during the period between May 1990 and September 1993. The following subjects were ineligible: those with a history of myocardial infarction, coronary

Table 1 Adjusted Relative Risks of Coronary Heart Disease Events According to Selected Factors*

Variable	*No. of men*	*No. of cases*	*Adjusted RR (95% CI)*
Baseline TC (mg/dl)			
<240	*1,463*	*29*	*1.00 (referent)*
240–259	*1,538*	*47*	*1.38 (0.86–2.22)*
≥260	*1,348*	*47*	*1.49 (0.89–2.49)*
Follow-up TC (mg/dl)			
<220	*2,097*	*50*	*1.00 (referent)*
220–239	*1,338*	*34*	*1.18 (0.75–1.84)*
≥240	*914*	*39*	*2.07 (1.31–3.29)*
HDL cholesterol (mg/dl)			
<40	*970*	*26*	*1.00 (referent)*
40–59	*2,485*	*81*	*1.27 (0.82–1.99)*
≥60	*894*	*16*	*0.74 (0.39–1.39)*
Body mass index (kg/m²)			
<22.5	*1,197*	*37*	*1.00 (referent)*
22.5–24.9	*1,609*	*39*	*0.84 (0.53–1.33)*
≥25.0	*1,543*	*47*	*1.06 (0.67–1.66)*
Angina pectoris			
None	*3,930*	*94*	*1.00 (referent)*
(+)	*419*	*29*	*2.62 (1.71–4.01)*
Diabetes mellitus			
None	*3,325*	*77*	*1.00 (referent)*
(+)	*1,024*	*46*	*2.02 (1.39–2.92)*
Hypertension			
None	*2,445*	*58*	*1.00 (referent)*
(+)	*1,904*	*65*	*1.32 (0.91–1.90)*
Cigarettes per day			
0	*2,679*	*76*	*1.00 (referent)*
1–19	*474*	*18*	*1.26 (0.75–2.13)*
≥20	*1,196*	*29*	*1.04 (0.67–1.62)*
Alcohol use (days/week)			
0	*1,683*	*56*	*1.00 (referent)*
1–4	*910*	*26*	*0.90 (0.56–1.45)*
≥5	*1,756*	*41*	*0.80 (0.53–1.22)*

RR, relative risk; CI, confidence interval; TC, total cholesterol.
**Based on Cox proportional hazards model controlling for age (5-year class), prior use of cholesterol-lowering drugs, statin use in the follow-up, and listed variables.*

bypass surgery, coronary angioplasty, or stroke; those with serum high-density lipoprotein (HDL) cholesterol of 80 mg/dl or greater; and those having life-limiting morbid conditions such as severe renal or hepatic disease. Each physician was instructed to randomly allocate patients to either pravastatin treatment or conventional treatment as specified in a sealed envelope, but participating physicians did not necessarily follow the instruction of the random assignment![9] Pravastatin was prescribed at a dosage of 10–20 mg/day, and the conventional treatment included dietary and/or exercise therapy and medication with hypolipidemic drugs other than probucol, bezafibrate, and statins. The patients were followed up until the end of 1997. Methodological issues relevant to the present study are described below.

Subjects

The present analysis included 4,349 of the 5,640 enrolled men; 1,291 were excluded for the following reasons: withdrawal of consent (n=147), no institutional contract (n=616), delayed discovery of ineligibility (n=97), and missing values for covariates (n=431). The category of 'no institutional contract' resulted from the introduction during the course of the study of a new regulation for clinical trials, which required a written agreement of contract between a participating institution and a sponsoring pharmaceutical company.

Laboratory and Clinical Data

Serum TC, HDL cholesterol, triglycerides, and other clinical and biochemical variables were determined at baseline and again after follow-up. Laboratory measurements were done at different laboratories, but each study physician was requested to use the same laboratory throughout the study period. Average serum TC concentrations during the follow-up were determined on the basis of periodic measurements at 3 months, 6 months, and every year thereafter. Serum HDL cholesterol was not measured during the follow-up for no less than 10% of the study subjects, and only baseline HDL cholesterol was used in the present study.

Hypertension was defined as present if a patient had systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg or if he was under medication for hypertension. Subjects were defined as having diabetes mellitus if they had either a fasting plasma glucose ≥140 mg/dl or hemoglobin A1c ≥6.5% or if they were under medication for diabetes mellitus. The presence of angina pectoris and prior use of hypolipidemic drugs were based on the report of study physicians. Statin use was defined if any statin drugs were prescribed during the follow-up period. Body mass index (kg/m²) was used as an index of obesity. Current habits of smoking and alcohol drinking were ascertained, and the number of cigarettes smoked per day and frequency of alcohol drinking per week were determined.

Table 2 Adjusted Relative Risks of Coronary Heart Disease Events According to Selected Factors in Men Aged Less Than 65 Years and Older Men*

Variable	<65 years (n=3,115)		≥65 years (n=1,070)	
	No. of cases	Adjusted RR (95% CI)	No. of cases	Adjusted RR (95% CI)
Baseline TC (mg/dl)				
<240	*18*	*1.00 (referent)*	*11*	*1.00 (referent)*
240–259	*27*	*1.34 (0.72–2.47)*	*20*	*1.51 (0.71–3.23)*
≥260	*32*	*1.69 (0.88–3.26)*	*15*	*1.26 (0.54–2.94)*
Follow-up TC (mg/dl)				
<220	*34*	*1.00 (referent)*	*16*	*1.00 (referent)*
220–239	*17*	*0.72 (0.40–1.31)*	*17*	*2.45 (1.20–4.98)*
≥240	*26*	*1.59 (0.90–2.81)*	*13*	*3.20 (1.44–7.09)*
HDL cholesterol (mg/dl)				
<40	*18*	*1.00 (referent)*	*8*	*1.00 (referent)*
40–59	*50*	*1.04 (0.60–1.78)*	*31*	*1.78 (0.80–3.93)*
≥60	*9*	*0.69 (0.30–1.56)*	*7*	*0.91 (0.32–2.60)*
Body mass index (kg/m²)				
<22.5	*22*	*1.00 (referent)*	*15*	*1.00 (referent)*
22.5–24.9	*23*	*0.65 (0.36–1.17)*	*16*	*1.11 (0.54–2.28)*
≥25.0	*32*	*0.85 (0.49–1.49)*	*15*	*1.45 (0.68–3.11)*
Angina pectoris				
None	*61*	*1.00 (referent)*	*33*	*1.00 (referent)*
(+)	*16*	*2.81 (1.60–4.95)*	*13*	*2.35 (1.22–4.54)*
Diabetes mellitus				
None	*43*	*1.00 (referent)*	*34*	*1.00 (referent)*
(+)	*34*	*2.36 (1.49–3.72)*	*12*	*1.46 (0.74–2.87)*
Hypertension				
None	*39*	*1.00 (referent)*	*19*	*1.00 (referent)*
(+)	*38*	*1.32 (0.83–2.10)*	*27*	*1.36 (0.73–2.52)*
Cigarettes per day				
0	*49*	*1.00 (referent)*	*27*	*1.00 (referent)*
1–19	*8*	*0.90 (0.42–1.91)*	*10*	*1.94 (0.91–4.13)*
≥20	*20*	*0.90 (0.53–1.54)*	*9*	*1.32 (0.60–2.89)*
Alcohol use (days/week)				
0	*30*	*1.00 (referent)*	*26*	*1.00 (referent)*
1–4	*18*	*1.02 (0.56–1.84)*	*8*	*0.67 (0.30–1.52)*
≥5	*29*	*0.85 (0.50–1.44)*	*12*	*0.71 (0.35–1.44)*

RR, relative risk; CI, confidence interval; TC, total cholesterol.
**Based on Cox proportional hazards model controlling for age (5-year class), prior use of cholesterol-lowering drugs, statin use in the follow-up, and listed variables.*

Follow-up

The end-point was a composite of CHD events comprising fatal and nonfatal myocardial infarction, coronary artery surgery, coronary angioplasty, CHD death, and sudden and unexpected death. The diagnostic criteria for these conditions were in accordance with those used in the Lipid Research Clinic Study?[22] Only definite cases of CHD events were used in the present study. These end-points were determined by the End-point and Adverse Effect Committee on the basis of periodic reports from the study physicians and the follow-up survey carried out from January to May in 1998.

As of the end of 1997, vital status was unknown for 36 men, and CHD events were not ascertained for 97 men. The average observation period was 5.03 years. There were 123 CHD events, including 66 cases of myocardial infarction, 11 cases of coronary bypass surgery, 24 cases of coronary angioplasty, 7 cardiac deaths, and 15 sudden deaths.

Statistical Analysis

The Cox proportional hazards model was used to examine the relation of clinical and behavioral factors to the risk of CHD events. The model included indicator variables for age (5-year class), use of statins, baseline serum TC (<240, 240–259, and ≥260 mg/dl), follow-up serum TC (<220, 220–239, and ≥240 mg/dl), baseline serum HDL cholesterol (<40, 40–59, and ≥60 mg/dl), body mass index (<22.5, 22.5–24.9, and ≥25.0 kg/m²), angina pectoris, hypertension, diabetes mellitus, prior use of lipid-lowering drugs, current smoking (0, 1–19, and ≥20 cigarettes per day), and current alcohol use (0, 1–4, and ≥5 days per week). Adjusted relative risk (RR) and 95% confidence interval (CI) were obtained from a regression coefficient and standard error for the corresponding indicator variable. Statistical significance was declared when the 95% CI did not include unity. Statistical computations were done by the SAS software version 8.2 (SAS Institute, Inc, Cary, NC, USA).

Results

The mean age of the study subjects at baseline was 58.0 years (SD 8.0). The average concentrations of baseline serum TC, follow-up TC, and baseline HDL cholesterol were 253 (SD 24.1), 221 (SD 26.2), and 49 (SD 12.0) mg/dl, respectively. The Pearson's correlation coefficient between baseline and follow-up TC was 0.39. The prevalence of diabetes mellitus was 23.5%, and that of hypertension was 43.8%. Men with angina pectoris and those who were overweight (body mass index ≥25) accounted for 9.6% and 35.5%, respectively. Proportions of smokers and men drinking alcohol once per week or more frequently were 38.4% and 40.4%, respectively.

Table 1 shows the relation of selected risk factors to CHD events in all subjects. Although the baseline serum TC was statistically nonsignificantly associated with a modest increase in the risk of CHD events, a statistically significant, 2-fold increase in the risk was observed for men with the highest concentrations of follow-up TC as compared with those with the lowest concentrations. A small, statistically nonsignificant decrease in the risk was observed for men with the highest concentrations of HDL cholesterol. Angina pectoris and diabetes mellitus were each associated with a statistically significant increase in the risk of CHD events. Hypertension was associated with a slightly increased risk of CHD events whereas body mass index showed no association with CHD events. Alcohol use was associated with a modest, statistically nonsignificant decrease in the risk, and cigarette smoking was unrelated to CHD events.

Table 2 presents results from the analysis stratified by age class. An increased risk of CHD events associated with elevated concentrations of follow-up TC was more marked in elderly men than in middle-aged men. In the latter group, the increase was modest, and statistically nonsignificant. On the other hand, a decrease in the risk associated with high concentrations of HDL cholesterol was almost limited to middle-aged men, although the decrease was not statistically significant. An increased risk associated with diabetes mellitus was also much greater in middle-aged men. A protective association with alcohol use was seemingly more evident in the elderly. Associations of angina pectoris and hypertension with CHD events did not differ in the 2 age groups.

Discussion

The present study showed that the serum TC concentration during the follow-up period, not at baseline, was related to an increased risk of CHD events in elderly men especially. This apparent difference in the association with TC between middle-aged and elderly men may be ascribed to random fluctuation in the sub-group analysis. Nonetheless, the present findings add to evidence that elevated concentrations of serum TC are an important risk factor for CHD in the elderly as well.

In a recent case-control study in Japan[4] hypercholesterolemia, which was defined as serum TC ≥220 mg/dl or use of cholesterol-lowering drugs, was associated with an increased risk of nonfatal myocardial infarction in those aged less than 65 years but not in older persons. Several prospective studies showed that elevated concentrations of TC was unrelated or more weakly related to the risk of CHD in older persons[11-13] The null or weak association between TC and CHD in older people was ascribed to comorbidity and frailty associated with low cholesterol in a prospective study[16] The finding in a randomized trial that statin use resulted in a measurable decrease in CHD events in older men and women strengthens the importance of hypercholesterolemia in the occurrence of CHD among elderly persons[17]

An inverse association between HDL cholesterol and CHD events was not substantial in the present study. High concentrations of serum HDL cholesterol are generally related to a decreased risk of CHD independently of TC or LDL cholesterol[3] although the protective association is not a universal observation[24,25] Exclusion of men with HDL cholesterol of 80 mg/dl or greater may partly explain the lack of a clear, protective association with HDL cholesterol in the present study. It may be more relevant that HDL cholesterol at baseline rather than during the follow-up was used. In the Japan Lipid Intervention Trial (J-LIT)[3] a cohort study of men and women under simvastatin treatment for hypercholesterolemia, high concentrations of HDL cholesterol during the treatment were associated with an evident decrease in the risk of CHD events.

The increased risk of CHD events associated with diabetes mellitus is consistent with the observation in the J-LIT[3] as well as with the current knowedge[23] However, the increased risk associated with diabetes mellitus was confined to middle-aged men. Insulin resistance is often accompanied by low HDL cholesterol, and part of the protective association between HDL cholesterol and CHD may be a reflection of the relation between insulin resistance and CHD[23,26] In this regard, the apparently stronger, positive association with diabetes mellitus in middle-aged men is compatible with a decreased risk associated with high concentrations of HDL cholesterol observed almost exclusively in this age group. However, these different associations with diabetes mellitus and HDL cholesterol according to age groups need confirmation because the confidence intervals of the RRs estimated for diabetes mellitus and the highest concentrations of HDL cholesterol in the 2 age groups overlapped well.

Hypertension was not appreciably associated with CHD events in either middle-aged or elderly men, which is not surprising. Hypertension has been well recognized as a risk factor for cardiovascular diseases, and effective medication for the condition is used in routine clinical practice. Patients under treatment for hypercholesterolemia were probably well treated for co-existing hypertension. A population survey in Japan showed that hypertensives on drug were more frequent in men with hypercholesterolemia under medication than in those without[27] However, hypertension ascertained at baseline was associated with a statistically significant, 2-fold increase in the risk of CHD events in the J-LIT[3]

The present findings regarding alcohol use were in line with a protective association between alcohol use and CHD[28] Cigarette smoking was not materially associated with CHD events. In addition to the fact that past smokers were not distinguished from lifelong nonsmokers, it is possible that smoker patients under treatment for hypercholesterolemia may have been more likely to quit smoking or to reduce the amount of cigarettes.

The present study examined risk factors for CHD events in men undergoing treatment for moderately elevated concentrations of TC, and the findings are not generalized to all Japanese men. The reported magnitudes in the risk of CHD events associated with risk factors were probably underestimated because of treatment for comorbid conditions and a change in lifestyle during the treatment. However, the present findings have practical implications in the management of patients with hypercholesterolemia. Diabetes mellitus, as well as the serum TC concentration under treatment, was found to be highly predictive of CHD events, and more importantly diabetes mellitus was not as appropriately treated as hypertension.

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Appendix 1

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RESEARCH COMMUNICATION

A Case-Control Study of Colorectal Cancer in Relation to Lifestyle Factors and Genetic Polymorphisms: Design and Conduct of the Fukuoka Colorectal Cancer Study

Suminori Kono, Kengo Toyomura, Guang Yin, Jun Nagano, Tetsuya Mizoue

Abstract

A case-control study was designed to elucidate roles of dietary and other behavioral influences, in combination with genetic susceptibility factors (genetic polymorphisms), in colorectal carcinogenesis. Both cases and controls were residents in Fukuoka City and three adjacent areas. Cases were patients undergoing surgery for a first diagnosis of colorectal cancer at 8 hospitals in the study area, and controls were randomly selected in the community by frequency-matching with respect to the expected distribution by sex, age (10-year class), and residence. Dietary and other lifestyle factors were ascertained by in-person interview, and venous blood was obtained for genotyping and possible biochemical measurements. The cases were interviewed at each hospital during the period from 2000 to 2003, and controls were surveyed during the period from 2001 to 2002. A total of 840 cases of colorectal cancer and 833 controls were interviewed with participation rates of 80% for the cases and 60% for the controls. Informed consent to genotyping was obtained from 685 cases and 778 controls. Further details of the design and conduct are described with respect to methodological aspects.

Key Words: Colorectal cancer - design - lifestyle factors - genetic polymorphisms - Japan

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Introduction

Colorectal cancer is one of the most common cancers in the world, accounting for nearly 10% of all incident cases (Parkin et al., 2001). In Japan, mortality from colorectal cancer, especially from colon cancer, has increased markedly in the past 50 years (Kono, 1996; Kono and Ahn, 2000), and Japan is currently among the countries with the highest incidence rates of colorectal cancer worldwide (Parkin et al., 2002). Dietary factors have long been implicated in the etiology of the disease, but unequivocal epidemiological evidence remains elusive. The increasing trend of colorectal cancer in Japan has generally been ascribed to the shift to a westernized diet characterized by high intake of fat and meat (Kono, 1996). As extensively reviewed in the report of World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR), however, fat intake has been generally found to be unrelated to the risk of colorectal or colon cancer in cohort and case-control studies (WCRF/AICR, 1997). On the other hand, it has been concluded that red meat probably confers increased risk of colorectal cancer (WCRF/AICR, 1997). Although expert panels are in agreement that vegetables are protective against colorectal cancer (WCRF/AICR, 1997; WHO Consensus Panel, 1999), change in vegetable consumption can not explain the increase in colon cancer incidence over time in Japan (Kono and Ahn, 2000). While a low intake of dietary fiber has also attracted much interest in research into the etiology of colorectal cancer, the evidence is not consistent (WCRF/AICR, 1997). The average consumption of dietary fiber earlier in Japan did not differ from the intake in Britain or Denmark with much higher rates of colorectal cancer (Kuratsune et al., 1986).

While several epidemiologic studies have investigated the roles of dietary factors in colorectal carcinogenesis in Japan, none has quantitatively focused on the relation of specific foods and nutrients to the risk of colorectal cancer. We therefore are now conducting a case-control study to investigate comprehensively the relation of lifestyle and genetic factors to colorectal cancer in Fukuoka, Japan. Our

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primary aim was to clarify roles for meat, fat, vegetables, and fiber in the development of colorectal cancer, but the study was also designed to address associations with other dietary and non-dietary factors as well. Possible protective factors unique to the Japanese diet such as green tea and soy foods are of particular interest (Kono, 1992; Yamane et al., 1996; Toyomura and Kono, 2002). Other targets include genetic polymorphisms linked with the metabolism of carcinogens or protective compounds (Vineis et al., 1999) and their interactions with dietary factors. This paper describes methodological aspects in the design and conduct of the study.

Study Design

Overview

This case-control study was designed to elucidate roles of dietary and other behavioral factors and genetic susceptibility factors (genetic polymorphisms) in colorectal carcinogenesis. Both cases and controls were residents in Fukuoka City and three adjacent areas. Cases were patients undergoing surgery for a first diagnosis of colorectal cancer, and controls were randomly selected from the community by frequency-matching with respect to sex, age (10-year class), and residence (Fukuoka City or the adjacent areas). Dietary and other lifestyle factors were ascertained by in-person interview, and venous blood was obtained for genotyping and possible biochemical measurements.

Size of the Study

The study aimed to recruit 500 cases of colorectal cancer and 1,000 controls. In determining the sample size, we first assumed detection of at least a 2-fold difference in the odds ratios for the highest versus lowest quartile of an exposure under study (such as fat and meat intake) at the two-sided significance level of 0.05 with a detection power of 80%. It was then calculated that at least 272 cases and 272 controls were required; the estimated size was 136 in each group when the prevalence of the exposure was 50%, and this number was doubled with allowance for the middle 50%, i.e. the second and third quartiles. With the prevalence of a factor under study at 5% in the population, the required numbers of cases and controls were estimated to be 515 each. Based on these preliminary estimations, we considered that 500 cases of colorectal cancer and 1,000 controls would be necessary for investigation of associations with rare genetic polymorphisms and interactions. A study of 500 cases and 1,000 controls corresponds to one with 660 cases and 660 controls with the same significance level and power.

Selection of Cases

Cases were a consecutive series of patients with histologically confirmed colorectal adenocarcinomas who were admitted to two university and affiliated hospitals for the first-time surgical treatment. Other eligibility criteria included the following characteristics: age of 20-74 years at the time of diagnosis; residence in Fukuoka City or three adjacent areas (Chikushi, Kasuya, and Itoshima); no prior history of partial or total removal of the colorectum, familial adenomatous polyposis (FAP), or inflammatory bowel disease; and mental and physical competence to give informed consent and to complete the interview.

Selection of Controls

Eligibility criteria for controls were the same as described for the cases except for two conditions, i.e. having no diagnosis of colorectal cancer and age of 20-74 years at the time of selection. It was decided a priori to select 1,500 persons as control candidates by two-stage random sampling, with two thirds of them expected to actually participate in the study. Numbers of control candidates by sex and 10-year age class were determined in proportion to numbers of incident cases of colorectal cancer by sex and 10-year age class in the study area, which were estimated from incidence rates in the Osaka cancer registry during the period 1988 to 1992 (Parkin et al., 1997). The first step was a random selection of 15 small areas which roughly corresponded to primary-school zones, and residents were randomly selected in each of these using the municipal resident registry, with allowance for proportions of residents for each small area by sex and 10-year age class.

Lifestyle Questionnaire

The questionnaire was developed for research nurses to perform a uniform interview with cases and controls regarding multifaceted lifestyle factors. The questionnaire used for the cases slightly differed from that of the controls in that the former included questions regarding the symptoms or screening leading to the diagnosis of colorectal cancer. The cases were asked whether symptoms or screening were events leading to the diagnosis, and if so the duration in months from the onset of symptoms or the time of the screening to the interview. The cases were carefully asked to answer to each question about their lifestyle habits and physical conditions in the period before the onset of the symptoms or the screening. Most of the questions were closed-ended, and open-ended questions were used for quantitative measures such as amount of alcohol and time spent in physical activities. Demographic information was confined to sex, date of birth, and area of residence.

Anthropometric questions inquired about height (cm), recent body weight (kg), and body weight 10 years before symptoms or screening in the cases and before the interview in the controls. Recorded heights and body weights were also obtained if they were available.

Questions on physical activities elicited type of job, activities in commuting and housework shopping, and leisure-time activities 5 years previously. As regards type of job, 5 options were prepared: sedentary or standing work (clerical work, taxi driving, housework, etc), work with walking (delivery by walking, patrolling on foot, etc), labor work (construction work, agricultural work, load transport, etc), hard labor work (digging or chopping with heavy tools, carrying heavy loads, etc), and no job (including students).

Weekly minutes spent in walking, bicycling, and jogging were each ascertained regarding commuting and housework shopping on average in the year. Regular leisure-time activities, on average over one year, were ascertained with regularity defined as at least once per week. For up to three activities, type, numbers of months and of days per week that individuals participated in each, and minutes of participation per occasion were reported. Intensity of each physical activity was determined in terms of metabolic equivalents (METs) on the basis of the published compilation of physical activities (Ainsworth et al., 1993), and MET-hours can be calculated as indices of non-occupational physical activities.

With regard to the smoking habit, individuals were first asked whether they had ever smoked cigarettes everyday for one year or longer. Then they were asked about the current status (before the symptom or screening in the cases). Age of starting smoking and that of quitting smoking (for past smokers) were ascertained, along with years of smoking and numbers of cigarettes smoked per day for each decade of age from the second to eighth decade.

Alcohol use until 5 years prior to the interview was elicited with alcohol use defined as drinking alcoholic beverages at least once per week over the period of one year or longer. Then individuals answered open-ended questions regarding the frequency of consumption (number of days per week) and amount of alcohol consumed on the day of alcohol drinking, on average over the year at the time of 5 years prior to the interview. The amount of alcohol was expressed by the conventional unit; one go (180 ml) of sake, one large bottle (633 ml) of beer, and half a go (90 ml) of shochu were each expressed as one unit; and one drink (30 ml) of whisky or brandy and one glass (100 ml) of wine were each converted to half unit. A supplementary question was asked about the psycho-social circumstances of drinking alcohol with four precoded answers: "for self-enjoyment or social events", "to pacify unhappy feeling", "unwillingly but for keeping acquaintance", and "for self-appreciation".

Prior histories of physician's diagnosis and surgeries included diabetes mellitus, gallstones, cholecystectomy, gastrectomy, colorectal polyp, colorectal polypectomy, large-bowel resection, appendicectomy, angina pectoris, myocardial infarction, cerebral infarction, femoral fracture, and other diseases leading to hospital admission. The time of diagnosis or surgery was elicited, and the related surgical scars were confirmed.

Use of vitamins, analgesics, and cholesterol-lowering drugs were recorded if these had ever been used at least once per week for a period of 6 months or longer. Activity of daily living was ascertained with classification of four categories (perfect independence, independence at home with need of help on the occasion of going outside, support needed at home, and bedridden). Also determined were parental history of colorectal cancer and the age of development of the disease.

Ten questions as to bowel habits were posed in a closed-ended fashion: frequency of bowel movement, frequency of feeling constipation, use of purgatives, regularity of bowel movement, time required for defecation, nature of stool, sense of residual stool, sense of bowel distension, frequency of fecal incontinence, and frequency of stool staining on the underwear.

Numbers of children, brothers, and sisters were reported. Women reported age of menarche, age of menopause, number of parity, and years after the last pregnancy. In addition to the interview on lifestyle factors, individuals were asked to complete a self-administered questionnaire containing 45 closed-ended questions regarding psychosocial stress and personality (Nagano et al., 2001).

Dietary Assessment

A PC-software package was developed for dietary assessment with support from an external laboratory (Core Create Systems, Kitakyushu). A total of 148 items of foods and beverages were selected with reference to the results from the national nutrition survey (Japan Ministry of Health, Labour and Welfare, 1999) and dietary questionnaires developed elsewhere in Japan (Tsubono et al., 1996; Tokudome et al., 1998). Frequency of consumption and portion size were elicited. Typical dishes were shown on the display, together with average portion sizes. Options for serving size were 0.5, 1, 1.5, and 2 with the displayed size as referent (average size) for most of the food items; more detailed options were prepared for the portion size of rice. Supplementary questions inquired about consumption of fatty portions of beef/pork and skin of chicken at table, consumption of soup for noodle dishes, rank of consumption as to 5 types of hot-pot dish cooked at the table, consumption pattern of vegetables and meat in hot-pot dishes, and use of sugar for coffee and black tea.

Ethical Considerations

The study protocol was approved by the ethical committees of Kyushu University and of all but two of the participating hospitals; the two hospitals had no ethical committee at the time of the survey, and approval was obtained from the director of each hospital. The objectives and overall design of the study were explained verbally to each potential case or control subject with the explanatory document shown, and a consent form was presented to him or her. Consent was sought for participation in the interview, genotyping, biochemical measurement, and a self-administered questionnaire on psychosocial stress and personality separately. The interview was started after he/she signed the consent form. A carbon copy of the signed form together with the explanatory document was handed to the participant.

Conduct of the Survey

Overview

A total of 840 cases of colorectal cancer and 833 controls were interviewed with participation rates of 80% and 60%, respectively. Gender, age, residence area, and consent to

genotyping are summarized in Table 1. Six research nurses were in charge of the interviews of both cases and controls, and one research clerk was involved in the recruitment of controls and monitored the progress of the survey.

Survey of Cases

The cases were interviewed in the wards of each hospital during admission. Research nurses visited each hospital weekly, and determined eligibility of cases by referring to admission logs and medical records. They then contacted each eligible patient with permission from the attending doctor, and interviewed him/her if written informed consent was given. A co-investigator at each hospital was in charge of supervising the survey of the cases. The survey started at two university hospitals and three affiliated hospitals in September or October in the year 2000 and at another three affiliated hospitals in May in the year 2001. The survey ended in December, 2003. At one university hospital, the survey at one of the two wards accommodating fewer surgical cases of colorectal cancer was delayed until December, 2002.

In the consecutive series of potentially eligible 1099 cases, 19 were found to be mentally incompetent; 23 had no histological diagnosis of colorectal adenocarcinomas; 3 were found to have a history of large-bowel resection after the interview; and one had FAP. After exclusion of these 46 cases, 840 (80%) of the 1053 eligible cases participated in the interview, and 685 (82%) gave informed consent to genotyping. Reasons for not participating in the study were patient's refusal (n = 115), physician's refusal (n = 46), and missing contact (n = 52). Five patients had previously been interviewed as controls in this study, and one of them had refused participation. The other four were not approached intentionally. Participation rates by sex and 10-year age class are shown in Table 2. Elderly patients were less likely to take part than younger adults, and the overall participation rate was slightly better in men than in women. It was later noticed that one interviewed case was aged 75 years at diagnosis, and this case was included in the study.

The occurrence of a relevant symptom resulted in the diagnosis of colorectal cancer for 556 cases, and screening was the event leading to diagnosis in 284 men. The duration from the onset of a symptom or screening until the interview ranged 0 to 36 months with a median of 2 months; the duration exceeded 12 months in 15 cases. The interview was conducted before the surgery in 551 cases (66%). Numbers of interviewed cases according to the location of the colorectal cancer were as follows: proximal colon 191, distal colon 279, rectum 354, and multiple sites 16. Cecum, ascending colon, and transverse colon were combined as proximal colon, and distal colon included descending and sigmoid segments.

Table 1. Overview of the Survey of Cases and Controls

	Cases	Controls
Number of subjects interviewed	840	833
Participation rate	80%	60%
Numbers of men/women	501/339	515/318
Mean age (range)	61 (27-75)[a]	59 (22-74)[b]
Residence in Fukuoka City	61%	65%
Length (min) of interview, median (range)	50 (27-105)	52 (25-133)
Number of consent to genotyping	685	778

[a] Age at diagnosis. One interviewed case aged 75 years was included.
[b] Age at random sampling.

Survey of Controls

In the random selection of 15 small areas in the study area, primary-school zones were preliminary reviewed with respect to location and population size. After merging sparse-population school zones and slight modification with allowance for administrative zones, 145 primary-school zones in Fukuoka City and 93 primary-school zones in the adjacent areas were restructured to 115 and 63 small areas, respectively. Population at the age of 20-74 years was twice larger in Fukuoka City than in the adjacent three areas, and thus we decided to select 10 small areas in Fukuoka City and 5 small areas in the adjacent areas and 1,000 residents in the former and 500 residents in the latter. Numbers of residents by sex and 10-year age class in each small area were determined on the basis of proportions of residents among those in the total of 10 small areas in Fukuoka City or the total 5 small areas in the adjacent areas by sex and 10-year age class. The number of residents selected in the small areas ranged from 66 to 143.

Recruitment and survey were initiated by a letter of invitation, sent to each control candidate, and a telephone call was made if the candidate was listed in the telephone

Table 2. Participation of Cases in the Interview Survey by Sex and Age Class

	Men		Women		Both	
Age (yr)*	No.[a]	%	No.	%	No.	%
20-29	-	-	2/3	67	2/3	67
30-39	8/9	89	7/7	100	15/16	94
40-49	44/52	85	35/38	92	79/90	88
50-59	147/173	85	111/137	81	258/310	83
60-69	204/249	82	117/161	73	321/410	78
70-75	98/131	75	67/93	72	165/224	74
Total	501/614	82	339/439	77	840/1053	80

* Age at diagnosis. - Numbers of participants/eligible persons.

directory. Two letters of invitation were additionally mailed to non-respondents. After completion of the survey in the 15th small area, a letter requesting participation was sent to 193 persons who had not responded to the third mail and 375 persons who had once refused the participation without hostility or explicit reluctance. In response to this final invitation, 10 (5%) of the former and 23 (6%) of the latter participated in the study.

The mail invitation revealed that a proportion of the control candidates were actually ineligible for the study for the following reasons: death (n = 7), migration from the study area (n = 22), undelivered mail (n = 44), history of large-bowel resection (n = 21), and mental incompetence (n = 19). Further, as mentioned above, there were participants who were diagnosed as having colorectal cancer after the survey (n = 5). After exclusion of these 118 persons, 833 (60%) of the 1382 eligible candidates were participants in the study. Overall, there was no response to the invitations by 158, and 391 persons refused. Participation rates by sex and 10-year age class are shown in Table 3. Women, especially in their 40s and 70s, were less willing to participate in the study than men. Consent to genotyping was obtained from 778 (93%) of the interviewed controls.

The survey was performed during the period from January 2001 to December 2002. The interviews of controls were conducted at community halls (n = 615), collaborative clinics (n = 170), the Department of Preventive Medicine at Kyushu University (n = 22), home (n = 14), work place (n = 8), and hospitals where control subjects were admitted (n = 4). An investigator physician attended to the survey at community halls, work place, and home. When the survey was done at a collaborative clinic, supervision was by a physician at the clinic. A gratuity of 5,000 Japanese yen was paid to each participant.

Validation Study of Dietary Assessment

A total of 60 men and women aged 40-64 years were asked to participate in a validation study. They were controls who participated in the survey in two small areas conducted from April to July in the year 2001. Of the 60 persons to whom requests were made, 36 agreed to participate in the validation study. They were asked to weigh (or record when weighing was not possible) foods and beverages consumed each day over one week each in four seasons (July-August 2001, October-November 2001, January-February 2002, and April-May 2002). In the course of the study, however, 8 persons withdrew, and only 28 persons completed the dietary record. In July, 2002, the interview was repeated using the same questionnaire and the PC software for dietary assessment. Results of the validation study will be published elsewhere.

Storage of Blood Samples

A vacuum tube containing EDTA-sodium was used to draw 5 ml of venous blood. Blood samples were stored temporarily in a refrigerator, and were centrifuged to separate plasma and buffy coat within the day of collection. Two aliquots of 1 ml plasma and buffy coat were stored at -80 °C. DNA was extracted from the buffy coat by using a commercial kit (QIAGEN GmbH, Hilden), and was stored at -40 °C. DNA concentrations ranged approximately from 50 to 150 ng/μl.

Informed Consent

Name and residence address of each participant were recorded on the signed form of informed consent, but not on the questionnaire. Only sex and date of birth were recorded. All of the signed forms of informed consent were transferred to the custody of the Kyushu University official in charge of protection of personal identification information. The questionnaire and blood sample were labeled with a unique anonymous number, which was recorded on the informed consent form as well.

Discussion

This is probably the fourth largest case-control study of colorectal cancer using community controls in the world. The larger investigations were a population-based study of 1993 cases and 2410 controls in the mainland of the United States (Slattery et al., 1997), 1192 pairs of cases and controls in Hawaii (Le Marchand et al., 1997), and 931 cases and 1552 controls in Shanghai (Chiu et al., 2003). While over 90% of the population was white in the study by Slattery et al (1997), the population was very diverse in ethnicity in Hawaii (Le Marchand et al., 1997). In the latter, Japanese,

Table 3. Participation of Controls in the Interview Survey by Sex and Age Class

	Men		Women		Both	
Age (yr)[a]	No[b]	%	No	%	No	%
20-29	2/8	25	6/9	67	8/17	47
30-39	21/30	70	17/29	59	38/59	64
40-49	62/102	61	35/73	48	97/175	55
50-59	167/272	61	79/144	55	246/416	59
60-69	180/269	67	131/216	61	311/485	64
70-74	83/132	63	50/98	51	133/230	58
Total	515/813	63	318/569	56	833/1382	60

[a] Age at random sampling. [b] Numbers of participants/eligible persons.

who were the majority of the population, numbered 598 pairs of cases and controls. Numbers of cases and controls decreased substantially in the analysis of genetic polymorphisms; approximately 1500 cases and 1800 controls were included in a study by Slattery et al (1999), and around 500 cases and 600 controls remained in the study in Hawaii (Le Marchand et al., 2002). The size of study is particularly important in investigating the role of rare genotypes in the gene-environment or gene-gene interaction. High participation rates of both cases and controls are required in case-controls studies to reduce selection bias. In the present study, the participation rate was not as high in the controls as attained for the cases. It is generally difficult to attain a high participation rate for community controls. In the recruitment of controls in the present study, the invitation was repeated four times when responses were not obtained. The net participation rate, which was calculated after exclusion of ineligible persons, was 45.3% at the first invitation, and the rate increased by 10.1% after the second invitation, and by 1.3% after the third invitation. Together with the fourth mailing to non-respondents, we once repeated the invitation to those who had refused to participate. This final attempt further increased the participation by 2.4%. The invitation repeated after the second was less efficient, but the participation rate of 60% was only achieved with the third and fourth attempts. Although a higher participation rate would of course be desirable, a rate of 60% is considered to be acceptable (Olson, 2001). The participation rates of controls were 64% in the above-mentioned largest study in the United States (Slattery et al., 1997), 71% in Hawaii (Le Marchand et al., 1997), and 85% in Shanghai (Chiu et al., 2003).

While we attained a fairly good participation of cases, consideration is needed with respect to their representativeness. The survey of cases was not performed at all hospitals in the study area where surgical treatment for colorectal cancer is performed. In particular, there are two other large hospitals located in the same area. However, it is unlikely that the patients included in the present study did differ from those at the other hospitals. We confined the eligible cases to those undergoing surgery for the purpose of mitigating psychological stress on both patients and interviewers. This was probably one reason for the high participation, but we missed some cases with advanced colorectal cancer. The interview of the cases during the admission may have been another reason for the high participation of 80%, and this procedure had another methodological advantage of shortening the period from disease onset to interview. Population-based case-control studies usually rely on information from cancer registries, and the interview is delayed much longer after the onset of the disease.

To our knowledge, 8 case-control studies have hitherto addressed the relation between food consumption and colorectal cancer in Japan. In three (Kato et al., 1990; Hoshiyama et al., 1993; Nishi et al., 1997), controls were recruited in the community and the participation rate was reported in only two studies (Kato et al., 1990; Hoshiyama et al., 1993). The earliest study was that conducted by Wynder et al (1969), in which 107 cases and 307 controls were interviewed at two hospitals in Tokyo. Cases of colon cancer, but not of rectal cancer, tended to have a diet lower in rice and higher in fruit and milk. Kondo (1975) carried out an interview survey on 393 cases and 786 controls at three hospitals in Nagoya in the period 1967-1973. Using a questionnaire containing 107 food and beverage items, the author reported more frequent consumption of eggs and chicken in colon cancer patients and a higher frequency of foods high in carbohydrate and low in animal protein in cases of rectal cancer. Haenszel et al (1980) surveyed 588 colorectal cancer patients and 1,176 hospital controls in Hiroshima, Aichi, and Miyagi Prefectures. They included over 100 food items in the questionnaire used for interview, but found no material association with most of the foods and beverages except for inverse associations with a few vegetables. Watanabe et al (1984) conducted a study of 203 matched-pairs at five hospitals in Kyoto, Shiga, and Hyogo Prefectures in the period 1977-1983, and noted a suggestive protective association with tofu and beans combined for rectal cancer. Tajima and Tominaga (1985) conducted a study of 93 cases and 186 controls at Aichi Cancer Center Hospital in the period 1981-1983. High consumption of chicken, pork, and beef were each associated with statistically significant or non-significant increase in the risk of colon and rectal cancer. Kato et al (1990) used a self-administered questionnaire, which elicited the consumption of 25 foods, in a study of 221 cases at Aichi Cancer Center Hospital during the period 1986-1990 and 586 controls randomly selected from telephone directories. The controls were respondents to a mailed questionnaire, and the response rate was 91%. Daily intake of meat was related to decreased risks of colon and rectal cancer. Hoshiyama et al (1993) carried out a study of 181 cases admitted to Saitama Cancer Center Hospital during the period of 1984-1990 and 653 community controls. The controls were 27% of residents randomly selected in the vicinity of the Hospital using the electoral rolls. Of 24 food items under study, seaweed consumption was inversely associated with both colon and rectal cancer, and pickled vegetables showed a positive association with rectal cancer. In the study reported by Nishi et al (1997), 330 cases and 660 community controls were interviewed in Hokkaido during the period 1987-1990, with controls randomly selected from telephone directories. Of 19 food items under study, visceral meat and ham/sausage were each associated with increased risks of colon and rectal cancer.

While several cohort studies have been documented regarding the relation of smoking or alcohol use to colorectal cancer in Japan (Kono et al., 1987; Hirayama, 1990; Shimizu et al., 2003; Otani et al., 2003), prospective data regarding diet and colorectal cancer in Japan are only available from the Hirayama cohort study which ascertained consumption frequencies for 7 food items (Hirayama, 1990).

Epidemiological studies in recent years have added to