Discussion

The present study was the first that examined the relationship between a functional *CYP7A1* polymorphism and colorectal adenomas, and showed a statistically significant decrease in the risk of proximal colon adenomas, but not of distal colon and rectal adenomas, associated with the *CC* genotype of the *CYP7A1 A-203C* polymorphism. The findings are consistent with the recent observation in Japan that the *CC* genotype of this polymorphism is related to a decreased risk of proximal colon cancer exclusively,[19] and provide further evidence for the role of bile acids in colorectal carcinogenesis. Although the relationship between the *CYP7A1 A-203C* polymorphism and fecal or serum bile acids has not been investigated directly, individuals with the *CC* genotype probably have lower exposure to bile acids due to decreased activity of 7α-hydroxylase.[25] However, further studies are required to assess functionality of the *CYP7A1 A-203C* polymorphism. It is possible that this polymorphism does not directly modulate the gene expression. Another linked polymorphism in the *CYP7A1* gene may be of functional relevance to bile acid production.

The *CYP7A1 A-203C* polymorphism was first identified as a genetic determinant of plasma total and LDL cholesterol levels through sequential steps of sibling-pair linkage analysis, DNA sequencing and association studies within families and in unrelated individuals in the USA.[16] In that study, the *CC* homozygotes had higher levels of total and LDL cholesterol in plasma than the *AA* homozygotes. A supportive finding was reported for men but not for women in the Framingham Offspring Study.[17] In contrast, a study of Micronesian islanders showed no association between the *CYP7A1 A-203C* polymorphism and serum apolipoprotein B, a surrogate of LDL cholesterol.[18] In this regard, it is of interest whether serum cholesterol levels differ by the polymorphism in the present study subjects. A preliminary analysis showed no measurable variation in serum total cholesterol levels according to the *CYP7A1 A-203C* polymorphism; in the whole subjects excluding men under lipid-lowering medication (20 cases and 41 controls), adjusted means (and standard errors) of fasting total cholesterol concentrations for the *AA*, *AC* and *CC* genotypes were 203.1 (1.9), 202.5 (1.3) and 203.2 (1.8) mg/dL, respectively, after controlling for age, hospital, rank, smoking, alcohol use, body mass index and physical activity. This lack of association is not necessarily surprising because many other factors, including dietary fat, influence the between-individual variation in serum total and LDL cholesterol. Different dietary habits may have masked the genotype–lipid association in individuals.

Several lines of epidemiological evidence have suggested that bile acids may increase the risk of proximal colon cancer selectively. Patients with the gallbladder removed have an increased risk of proximal colon cancer.[26–28] Cholecystectomy results in increased fecal excretion of secondary bile acids due to an increase in the bile acid pool in the enterohepatic circulation and increased degradation of primary bile acids.[29,30]

Low concentrations of serum total or LDL cholesterol have been related to increased risk of colon cancer in many prospective studies.[31] Whereas this inverse association has generally been ascribed to the effect of preclinical cancer existing at the baseline,[31] an increased risk of proximal colon cancer associated with low cholesterol levels persisted 10–20 years later in a prospective study of Japanese people in Hawaii.[32] In a case-control study, lower levels of serum total and LDL cholesterol were observed in cases of proximal colon cancer alone than in controls.[33] In that study, individuals with the *E4* allele for apolipoprotein E, in whom bile acid synthesis is decreased,[34] had a lower risk of proximal colon cancer and adenomas.

The present study had methodological advantages in that colonoscopy was carried out non-selectively in a defined population and in that the absence of polyp lesions was confirmed in the control subjects by total colonoscopy. The study subjects were not representative of Japanese men in the general population, but selection was unlikely to exist with regard to the genetic polymorphism under study. The allele frequency of *CYP7A1-203C* (51%) in the control subjects in the present study was quite similar to that observed in a random sample of adult residents in an area in Japan (50%),[19] whereas these values are slightly greater than those reported in Caucasians (approximately 40%).[16,17] Lack of dietary information was a weakness in the present study. High-fat diet increases bile acid excretion,[35,36] and thus the interaction between the *CYP7A1 A-203C* polymorphism and fat intake deserves further studies. Another weakness was the small number in the subgroup analysis, especially regarding size-specific risks of proximal colon adenomas. Decreased risk of proximal colon adenomas associated with the *CC* genotype did not seem to differ by size, but the observed OR were variable. Moreover, it was uncertain whether the risk of proximal colon adenomas was decreased in individuals with the heterozygous *AC* genotype. Larger studies are required to address these questions conclusively.

In conclusion, a case-control study demonstrated a decreased risk of proximal colon adenoma in individuals with the *CC* genotype of the *CYP7A1 A-203C* polymorphism, which probably renders lower activity of the enzyme synthesizing bile acids. The findings add to evidence for the role of bile acids in colorectal carcinogenesis.

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Relation of alcohol use and smoking to glucose tolerance status in Japanese men ☆

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Abstract

To investigate the relation of alcohol use and cigarette smoking to glucose tolerance status, we performed a cross-sectional study of 3038 male officials aged 46–59 years in the Self-Defense Forces. Glucose tolerance status was determined by a 75-g oral glucose tolerance test. A self-administered questionnaire was used to ascertain alcohol use, smoking habits, and other lifestyle characteristics. Statistical adjustment was made for parental history of diabetes, body mass index, and leisure-time physical activity. Alcohol use was positively associated with impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes mellitus each. The association was dose-dependent, with odds of each category of glucose intolerance increased even among those with moderate alcohol use. Cigarette smoking was not related to any categories of glucose intolerance. Alcohol use may confer increased risks not only of type 2 diabetes mellitus but also of preceding glucose intolerance status. Smoking does not seem to deteriorate glucose tolerance.

Keywords: Alcohol; Smoking; Glucose intolerance; Cross-sectional study; Japanese men

1. Introduction

The prevalence of type 2 diabetes mellitus has increased and is becoming the great public health problem in many parts of the world [1]. Obesity and physical inactivity are well known to increase the risk of type 2 diabetes mellitus [2], but other factors associated with type 2 diabetes mellitus remain uncertain. Alcohol use has been a matter of interest in the epidemiology of type 2 diabetes mellitus. Moderate alcohol use was shown to be related to increased insulin sensitivity in several [3,4], but not all [5,6], studies. Epidemiologic findings are inconsistent regarding the relation between alcohol use and type 2 diabetes mellitus. While several prospective studies showed a protective association between moderate alcohol use and type 2 diabetes mellitus [7–11], others failed to find such an association [12,13]. Some studies observed an increased risk of type 2 diabetes mellitus associated with alcohol use [14–18].

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On the other hand, cigarette smoking was reported to be related to increased risk of type 2 diabetes mellitus in several studies [9,19–21].

Type 2 diabetes mellitus is a morbid condition of continuum, and impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) precede type 2 diabetes mellitus [22]. Not many studies have addressed the association of either alcohol use or cigarette smoking with the prediabetic conditions [23–26]. In this study, we investigated the relation of alcohol use and cigarette smoking to glucose tolerance status determined by a 75-g oral glucose tolerance test (OGTT) in middle-aged Japanese men.

2. Materials and methods

2.1. Study subjects

Subjects were male self-defense officials who received a preretirement health examination from January 1997 to March 2002 at the Self-Defense Forces (SDF) Fukuoka Hospital or the SDF Kumamoto Hospital. The preretirement health examination is a nationwide program, which offers a comprehensive medical examination for those retiring from the SDF. Details of the health examination have been described elsewhere [27,28].

In the consecutive series of 3416 men aged 46–59 years, a total of 3225 men were included in this study; 8 men refused to participate in the study, 17 men were undetermined as regards glucose tolerance status, and 166 men were excluded for the following reasons: endocrine diseases ($n = 15$), chronic pancreatitis ($n = 9$), chronic hepatitis or liver cirrhosis ($n = 78$), use of steroids ($n = 9$), past history of gastrectomy ($n = 56$), and missing information as regards covariates under study ($n = 4$); some men had two or more conditions for exclusion. Furthermore, 187 men with a history of dietary or drug treatment for type 2 diabetes mellitus were excluded irrespective of their glucose levels. Thus a total of 3038 men remained in the present analysis.

The study was approved by the ethical committee of the Kyushu University Faculty of Medical Sciences. All study subjects gave written informed consent prior to their participation in the study.

2.2. Laboratory methods

The routine medical examination included a 75-g OGTT during a 5-day admission among others. After an overnight fast, venous blood was drawn for measurement of plasma glucose before and 2 h after the oral challenge. Plasma glucose levels were assayed by the glucose oxidase method using commercial reagents (Shino Test Co. Ltd., Tokyo) at each hospital. Subjects were classified as having normal glucose tolerance, IFG, IGT, or type 2 diabetes mellitus by the World Health Organization (WHO) criteria revised in 1998 [22]. Body weight and height were recorded, and body mass index (BMI) (kg/m^2) was calculated as a measure of obesity.

2.3. Questionnaire

A self-administered questionnaire was used to ascertain alcohol use, smoking habits, leisure-time physical activity, and other lifestyle characteristics. Alcohol drinkers were defined as those who had drunk once a week or more over a period of 1 year or longer. Past drinkers were separated from lifelong nondrinkers. Current drinkers were asked about frequency and amount of consumption per occasion of five different alcoholic beverages (*sake*, *shochu*, beer, whiskey/brandy, and wine) on average in the past year, and their alcohol intake was estimated using the approximate volume concentration of alcohol in each beverage. The estimated intake of alcohol intake was found to be highly correlated with the intake based on the 28-day diet record in the past year; Spearman rank correlation coefficient was 0.91 [29]. Ever smokers were defined as those who had smoked one cigarette or more per day over a period of 1 year or longer. Past smokers were separated from never smokers. Current and past smokers reported the average number of cigarettes smoked per day and the total years of smoking.

Questions on leisure-time physical activity were slightly changed in April 1999. Before the revision, the subjects were first asked about the frequency on average in the past year of regular participation in recreational exercise and sport using a closed ended question (none, 1 to 2, 3 to 4, 5 to 6 times per week and daily). If the subjects participated in recreational physical activity once per week or more frequently, they reported the type of regular exercise or sport and the time spent per occasion. Up to three types of regular exercises were recorded. In the revised questionnaire, the subjects were first asked whether they participated in recreational activity regularly (one or more times per week) in the past year. Those with a regular participation reported up to three types of physical activities together with frequency per week and time spent per occasion for each activity. Reported type of exercise and sport was classified into light, moderate, heavy, or very heavy activity in accordance with the published energy expenditure requirements in terms of metabolic equivalent (MET) for different physical activities [30]. The time spent in recreational exercise was multiplied by the corresponding MET value (light 2, moderate 4, heavy 6, and very heavy 8) to yield an MET-hour score.

2.4. Statistical analysis

Multiple logistic regression analysis was used to examine the relation of alcohol use and cigarette smoking to glucose tolerance status in terms of odds ratios (ORs) of individual categories of glucose intolerance. Ordinal logistic regression was also applied with ordinal values (0, 1, 2, and 3) assigned to normal glucose tolerance, IFG, IGT, and diabetes, respectively. Statistical adjustment was made for hospital, rank in the

Table 1
Potential confounding variables according to alcohol use ($n = 3225$)

Variable	Never use	Past use	Alcohol (ml per day)		
			<30	30–59	60+
Number	455	96	815	923	936
Parental history of diabetes (%)	9.7	17.7	9.5	9.5	8.9
BMI (kg/m^2), mean (S.D.)	24.1 (2.8)	24.0 (3.3)	23.9 (2.7)	23.9 (2.5)	23.8 (2.5)
Current smoking (%)	52.1	52.1	38.7	46.5	53.2
Number of cigarettes per day, median (IQR)[a]	20 (20–30)	20 (20–30)	20 (20–25)	20 (20–25)	20 (20–30)
METs-hour per week, median (IQR)	10 (0–24)	12 (0–27)	16 (6–28)	16 (6–28)	16 (5–28)

S.D.: standard deviation; IQR: interquartile range.
[a] Current smokers only.

SDF, parental history of diabetes, BMI, leisure-time physical activity, and alcohol intake or cigarette smoking. Age was in a limited range from 46 to 59 years, and 98% of the subjects were aged 50–54 years. Thus age was omitted in the present analysis. The 95% confidence interval (CI) of OR was estimated by using the standard error of a logistic regression coefficient for each indicator variable.

Alcohol use was categorized into five groups (never, past, and current drinking with a consumption of <30, 30–59, or 60+ ml of alcohol per day). Cigarette smoking was categorized into five categories (never, past, and current smoking with a consumption of <15, 15–24, or 25+ cigarettes per day). BMI was classified at the cut off points of the 25, 50, and 75th percentiles in the distribution. Rank in the SDF was divided into three classes (low, middle, or high), and leisure-time physical activity into four levels (no regular exercise and tertiles of MET-hours per week in regular participants). Indicator variables representing categories of the above-mentioned factors were included in the logistic regression models as independent variables.

The trend of the association with alcohol use or cigarette smoking was assessed by using multiple logistic regression with ordinal scores (0, 1, 2, and 3) assigned to four levels of alcohol use or cigarette smoking after exclusion of past drinkers or past smokers. Two-sided p values less than 0.05 were regarded as statistically significant. All analyses were performed using the Statistical Analysis System (SAS) version 6.12 (SAS Institute, Inc., Cary, NC).

3. Results

Of the 3038 men, there were 204 (7%) prevalent cases of IFG, 568 (19%) of IGT, 171 (6%) of newly diagnosed type 2 diabetes mellitus.

Table 1 shows distributions of the covariates according to categories of alcohol use. Current smoking was more frequent with increasing levels of alcohol consumption. Physical exercise during leisure-time was greater in current drinkers than in never and past drinkers. Neither parental history nor BMI was measurably correlated with alcohol use. On the other hand, mean BMI was lower in current smokers regardless of the number of cigarette per day. Physical exercise during leisure-time decreased progressively with increasing levels of cigarette smoking (Table 2).

Table 3 presents adjusted ORs of IFG, IGT, and type 2 diabetes mellitus each in relation to levels of alcohol drinking and cigarette smoking. Alcohol use was positively associated with IFG, IGT, and type 2 diabetes mellitus each with a statistically significant trend. The ordinal ORs of glucose intolerance increased gradiently with increasing amounts of alcohol intake. Cigarette smoking was not measurably related to any of the three categories of glucose intolerance. Nor did the ordinal

Table 2
Potential confounding variables according to cigarette smoking category ($n = 3225$)

Variable	Never smoking	Past smoking	No. of cigarettes per day		
			<15	15–24	25+
Number	841	855	100	920	509
Parental history of diabetes (%)	8.8	10.2	9.0	9.0	11.0
BMI (kg/m^2), mean (S.D.)	24.1 (2.4)	24.2 (2.4)	23.5 (3.1)	23.6 (2.8)	23.6 (2.7)
Current alcohol use (%)	80.4	88.4	84.0	81.6	80.0
Alcohol (ml per day), median (IQR)[a]	36 (18–61)	46 (27–72)	45 (19–72)	47 (27–72)	58 (35–90)
METs-hour per week, median (IQR)	16 (7–29)	17 (7–29)	16 (5–32)	13 (3–26)	10 (0–22)

S.D.: standard deviation; IQR: interquartile range.
[a] Current alcohol users only.

Table 3
Adjusted odds ratios and 95% confidence intervals of glucose tolerance status according to alcohol use and cigarette smoking

Variable	No. of controls	IFG		IGT		Type 2 diabetes mellitus		Ordinal class of glucose intolerance	
		No.	OR (95% CI)[a]	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]	No.	OR (95% CI)[a]
Alcohol (ml per day)									
Never use	340	14	1.00 (referent)	65	1.00 (referent)	10	1.00 (referent)	89	1.00 (referent)
Past use	61	5	2.12 (0.72–6.18)	13	1.08 (0.55–2.09)	6	3.27 (1.12–9.54)	24	1.56(0.92–2.63)
<30	536	40	1.86 (0.99–3.51)	136	1.38 (0.99–1.93)	50	3.70 (1.83–7.50)	226	1.78 (1.34–2.36)
30–59	588	62	2.50 (1.36–4.58)	173	1.59 (1.15–2.20)	48	3.16 (1.56–6.41)	283	1.94 (1.47–2.56)
60+	570	83	3.57 (1.98–6.46)	181	1.75 (1.27–2.42)	57	3.93 (1.96–7.91)	321	2.25 (1.71–2.96)
Trend[b]			$p < 0.0001$		$p = 0.0005$		$p = 0.002$		$p < 0.0001$
Cigarettes per day									
Never smoking	583	51	1.00 (referent)	133	1.00 (referent)	42	1.00 (referent)	226	1.00 (referent)
Past smoking	524	67	1.29 (0.87–1.91)	173	1.37 (1.05–1.78)	43	1.04 (0.66–1.63)	283	1.24 (1.01–1.54)
<15	62	6	1.24 (0.50–3.08)	16	1.18 (0.65–2.14)	9	2.17 (0.98–4.80)	31	1.47 (0.93–2.32)
15–24	595	58	1.13 (0.75–1.70)	161	1.21 (0.93–1.57)	45	1.15 (0.73–1.80)	264	1.16 (0.94-1.44)
25+	331	22	0.78 (0.46–1.34)	85	1.11 (0.81–1.52)	32	1.33 (0.80–2.20)	139	1.12 (0.87–1.45)
Trend[c]			$p = 0.46$		$p = 0.26$		$p = 0.40$		$p = 0.29$

OR: odds ratio; CI: confidence interval.
[a] Adjusted for hospital, rank, parental history of diabetes, BMI, leisure-time physical activity, and either alcohol intake or smoking.
[b] Past drinkers were excluded.
[c] Past smokers were excluded.

logistic regression analysis show an appreciable association between smoking and glucose intolerance.

4. Discussion

The present study showed positive associations of alcohol use with IFG, IGT, and type 2 diabetes mellitus independent of BMI, physical activity, and other confounding factors. Increased ORs of IFG, IGT and type 2 diabetes mellitus were observed not only in heavy drinkers but also in light (<30 ml per day) and moderate (30–59 ml per day) drinkers. The present findings suggest that alcohol use may be related to an increased risk of type 2 diabetes mellitus.

A fairly large number of prospective studies have addressed the relation between alcohol use and type 2 diabetes mellitus, but their findings are inconsistent [7–18]. Inconsistency is noted even among studies in Japan [7,11,17,18]. Two studies of Japanese showed a decreased risk for the consumption of 30–50 g in alcohol per day [7,11], the other two reported a positive association between alcohol use and type 2 diabetes mellitus [17,18]. A decrease in the risk of type 2 diabetes mellitus was observed not only in those with moderate consumption (10–49 g per day) but also in those with a relatively high consumption (≥50 g per day) in the Health Professional Follow-Up Study in the United States [8]. On the contrary, a community-based prospective study in the United States reported an evident increase in the risk of type 2 diabetes mellitus diagnosed by the glucose tolerance test in men with a high alcohol consumption (≥25 g per day), but not in women classified as those with high alcohol consumption (≥17 g per day) [14]. In Hispanic Americans [15], each consumption of 10 g in alcohol per week was associated with more than two-fold increase in the risk of developing type 2 diabetes mellitus in men but not in women. Another prospective study in the United States also reported a significantly increased risk of type 2 diabetes mellitus in men consuming 40 g or more alcohol per day as compared with the moderate drinkers (9–18 g per day) [16].

The inconsistency regarding alcohol use and type 2 diabetes mellitus in these prospective studies does not seem to be ascribed to different criteria for type 2 diabetes mellitus in different studies. The findings are disparate even among studies based on the same methods such as the American Diabetes Association criteria for fasting plasma glucose [7,11,16] and self-reported physician's diagnosis [8,9,18]. Furthermore, important confounding factors such as BMI and physical activity were adjusted for in most of the studies. The present study was cross-sectional in design, and thus the findings are less convincing as compared with those from the previous prospective studies. However, 75-g OGTT was used for determination of glucose tolerance status. Two of the three previous cross-sectional studies based on a 75-g OGTT found a significant positive association between alcohol use and type 2 diabetes mellitus [24,25], and the other found no measurable association [23]. Further studies are needed to clarify the association between alcohol and type 2 diabetes mellitus.

The above-mentioned three studies also examined the relation between alcohol use and IGT [23–25]. Moderate alcohol drinking was related to a decreased risk of IGT among Swedish men [24], but the other two studies failed to find any significant association [23,25]. In the present study, increased ORs associated with alcohol use were seemingly greater for IFG and type 2 diabetes mellitus than for IGT. This may have been due to chance fluctuation, because the 95% CIs of ORs well overlapped among the three categories of glucose intolerance.

Biological mechanisms regarding alcohol and glucose intolerance also remain unclear. Although some epidemiological and experimental studies suggested a beneficial effect of moderate alcohol use on insulin sensitivity [3,4], others failed to find such a beneficial effect [5,6]. Alcohol use was shown to exert a direct toxic rather than beneficial effect on the pancreas, and thereby yielding a defect in insulin secretion in animals [31,32], and alcohol was also shown to decrease glucose utilization in healthy men [33]. A recent study has noted a distinct difference in the insulin profile after glucose challenge between IFG and IGT [34]. Insulin resistance is a characteristic feature of IFG, while impaired insulin secretion is observable in individuals with IGT [34]. It is of interest to examine the insulin profile during the OGTT in relation to alcohol intake, but no such data were available in the present study.

In the present study, smoking was not clearly associated with any categories of glucose intolerance. Recently, several prospective studies have reported a positive association between cigarette smoking and type 2 diabetes mellitus [9,19–21]. In two studies, the increased risk was observed in the consumption of 15 or more cigarettes per day, but the increased risk was modest among current smokers with the consumption of 25 or more cigarettes per day [19,20]. On the other hand, the consumption of 31 or more cigarettes per day was associated with more than four-fold increase in the risk of developing type 2 diabetes mellitus in Japanese men [21]. In the Nurses' Health Study, an increase in the risk of type 2 diabetes mellitus was observed in those with a relatively light consumption (1–14 cigarettes per day) [9]. We have no clear explanation for the lack of association between smoking and type 2 diabetes mellitus in the present study.

The present study had several methodological advantages other than the use of 75-g OGTT. The number of subjects was fairly large, and the subjects were homogeneous in terms of social background as well as age range. Since the preretirement health examination program covered almost all men retiring from the Self-Defense Forces, selection bias was negligible. Lifestyles were ascertained before the results of medical examination were reported, and it is unlikely that men with glucose intolerance had changed their lifestyles. Although men with a history of dietary or drug treatment for diabetes mellitus were excluded, part of the study subjects may have been informed of hyperglycemia previously, because the annual health check-up including urine glucose test or measurement of fasting plasma glucose has been carried out in the Self-Defense Forces, as done at workplaces elsewhere in Japan. It is, however, unlikely that such individuals who were probably at high risk of glucose intolerance had increased alcohol consumption. Weakness of the cross-sectional study should be borne in mind when interpreting the present results, as mentioned above. Our study subjects were men serving for the SDF until retirement. The study subjects may differ from men in the general population in various lifestyle aspects. Our findings thus may not be directly generalized for the general population.

In conclusion, a cross-sectional study based on a 75-g OGTT showed a positive association between alcohol use and glucose intolerance and a null association between smoking and glucose intolerance. The role for alcohol use and smoking in the development of type 2 diabetes mellitus needs further clarification.

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Nutritional Epidemiology

Dietary Patterns and Glucose Tolerance Abnormalities in Japanese Men[1]

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ABSTRACT The Western dietary pattern appears to confer diabetes risk, but the role of dietary patterns in Asian populations remains unclear. We investigated the association between major dietary patterns and the glucose tolerance status of Japanese men. Abnormalities included impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes. Subjects were 2106 Japanese men who were administered a 75-g oral glucose tolerance test at their preretirement health check-ups. Information about diet was obtained using a 74-item FFQ before the test. Three dietary patterns were generated by factor analysis: *1*) a high-dairy, high-fruit and -vegetable, high-starch, low-alcohol pattern; *2*) an animal food pattern; and *3*) a Japanese pattern. We used logistic regression analysis to estimate odds ratios (OR) with adjustment for potential confounding variables. A significant inverse association was found for the high-dairy, high-fruit and -vegetable, high-starch, low-alcohol pattern (P for trend < 0.0001); the OR of having a glucose tolerance abnormality (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes) for the 2nd, 3rd, and 4th quartiles were 0.80 (95% CI = 0.62–1.04), 0.71 (95% CI = 0.54–0.92), and 0.51 (95% CI = 0.38–0.67), respectively, compared with the lowest quartile. The inverse association was consistent for each glucose tolerance abnormality as well as across subgroups stratified by risk factors for diabetes. The Japanese dietary pattern was positively associated with impaired glucose tolerance (P for trend = 0.048). A dietary pattern characterized by frequent consumption of dairy products and fruits and vegetables but low alcohol intake may be associated with a decreased risk of developing a glucose tolerance abnormality. J. Nutr. 136: 1352–1358, 2006.

KEY WORDS: • *dietary pattern* • *factor analysis* • *impaired fasting glucose* • *impaired glucose tolerance* • *type 2 diabetes*

The prevalence of type 2 diabetes is increasing worldwide (1). A recent Japanese survey showed that 9% of the adult population have known or suspected diabetes, and another 11% may also have diabetes (2). The age-specific prevalence of diabetes in Japanese subjects is slightly higher than that in European populations (3,4). The results of these surveys seem peculiar in light of the fact that obesity is not as prevalent in Japanese patients with type 2 diabetes as in Caucasian patients (5). This may be attributable in part to a high genetic susceptibility to type 2 diabetes of Japanese individuals (6); however, little is known about the role of diets typically consumed by the Japanese.

Analysis of dietary patterns has received much attention as a method of investigating the role of diet in studies of chronic diseases. Approaches of this sort, focusing on a combination of several foods, can overcome problems arising from the close intercorrelation and potential effect modulation among numerous foods or nutrients (7,8). Of factor-analysis studies among Western populations (9–12), some (11,12) indicated that a Western dietary pattern characterized by a greater consumption of high-energy, high-fat foods predicts diabetes risk. However, dietary patterns generated by factor analysis may differ across populations with different dietary cultures. The high consumption of rice, fish, and soybean products in Japan (13) suggests several different dietary patterns in Japanese populations.

The aim of the present study was therefore to investigate dietary patterns in relation to glucose tolerance status, using data from preretirement health examinations of Japanese men who were self-defense officials.

SUBJECTS AND METHODS

Study procedure. The data used were derived from the Self-Defense Forces Health Study, a cross-sectional survey of men who were self-defense officials and participated in a preretirement health check-up at 2 hospitals (Fukuoka and Kumamoto) in Japan. The study procedure was described elsewhere (14–16). Study questionnaires regarding smoking, drinking, leisure-time physical activity, diet, and other health-related information were distributed before the test to male examinees on d 1 of hospital admission for examination. For leisure-time physical activity, the men were asked about the weekly

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frequency and the duration of each activity on each occasion for up to 3 types of activity. Research assistants checked the questionnaire and, if necessary, sought clarification from the study subjects. Results of physical measurements and laboratory tests were extracted from clinical reports. Written informed consent was obtained from study participants. The study protocol was approved by the ethics committee of Kyushu University.

Study subjects. Among 2377 male self-defense officials who underwent the examination from April 1999 through March 2002, 2370 men aged 47–59 y (mean, 52.4 y) agreed to participate in the study. After excluding men with a history of cancer, stroke, myocardial infarction, coronary revascularization, inflammatory bowel diseases, colorectal surgery, or diabetes mellitus, 2141 men were included for the analysis of dietary patterns. After further exclusion of 35 men who had a history of gastrectomy, a condition that might affect the oral glucose tolerance test result, we analyzed the data for the remaining 2106 men to assess the association between dietary patterns and glucose tolerance status.

Glucose measurements. All officials undergo a comprehensive health examination before retirement; the exam includes a 75-g oral glucose tolerance test as a routine procedure. After an overnight fast, venous blood was drawn for measurement of plasma glucose before and 2 h after the oral glucose load. Examinees whose fasting plasma glucose concentration at admission was ≥7.0 mmol/L or who were under medical care for diabetes were not given an oral glucose tolerance test. Plasma glucose concentrations were measured by the glucose oxidase method using commercial reagents (Shino Test).

Dietary assessment. Information about diet was collected using a FFQ designed to assess the average intake of 74 foods, food groups, and food preparations over the previous year. The questionnaire was an expanded version of a 45-item FFQ that was developed on the basis of a published questionnaire (17) and was validated against four 7-d records, collected each season (18). The expansion of food items was done with reference to food consumption in the National Nutrition Survey (13) and a dietary questionnaire developed elsewhere in Japan (19). Participants were asked to choose from 7 response options for most dietary items, ranging from "never/<1 time/mo" to "2–3 times/d." Different response schemes were used for green tea, coffee, and rice (5 options), and alcoholic beverages (6 options). Daily consumers of green tea, coffee, or rice were asked about the number of cups or bowls consumed per day. Current drinkers, defined as those who consumed alcoholic beverages weekly for at least 1 y in their lifetime and who were drinking at the time of the survey, were asked about the frequency of consumption and the amount consumed per occasion of 5 alcoholic beverages, that is, sake (a Japanese wine), shochu (a Japanese distilled beverage), beer, whiskey, and wine. The amount consumed per occasion was used in the estimation of total ethanol intake from these alcoholic beverages, but only the frequency of consumption for each alcoholic beverage was used in the analysis of dietary patterns.

Before the analysis of dietary patterns, intakes of green tea, coffee, or rice were converted into units of cups or bowls per day, whereas those of other dietary items were quantified in terms of frequency per week. Five dietary questions that overlapped with or were duplicated by others (collective consumption of cooked vegetables, apple, tangerine, other orange, watermelon) and 3 questions about food spreads (butter, margarine, and jam/honey) were not included. Furthermore, some foods or food groups similar in nutritional contents or culinary use were combined (**Appendix** 1), leaving 39 food items for purposes of the present study.

Statistical analysis. The method used in generating dietary patterns and the naming of the derived patterns were described in our previous study of colorectal adenomas (16). Dietary patterns were generated by factor analysis (principal components). Factor analysis is a technique used to reduce a number of variables into fewer independent factors. To simplify interpretation, a linear transformation called a "rotation" is normally performed on the initial factor solution. We used an orthogonal rotation procedure (varimax rotation), which maintains the uncorrelated nature of the factors. In determining the number of factors to retain, we considered the scree test and interpretability. The scree plot and postrotated factor loadings revealed that 3 factors described comprehensively the distinctive dietary patterns of the study population. We thus retained the 3 patterns and designated them as follows: *1*) a high-dairy, high-starch, high-fruit and -vegetable, low-alcohol (DSFA)[3] pattern; *2*) an animal food pattern; and *3*) a Japanese pattern, according to the food items showing high loading (absolute value) with respect to each dietary pattern (**Table 1**). We confirmed that these dietary factors emerged when all 74 food items in our questionnaire were simply included in factor analysis and that patterns of loading with the dietary factors were similar among foods or food groups combined. A factor score for each dietary pattern was calculated by weighting standardized consumption of each food item by the corresponding factor loading and summing the resulting values. This score ranked individuals in terms of how closely they conformed to the dietary pattern.

The potential confounding variables considered were hospital (Fukuoka or Kumamoto), age (treated as a continuous variable), parental history of diabetes (absent or present), occupational rank (3 categories), BMI (continuous), smoking (lifetime nonsmoker, former smoker, and current smoker using <15, 15–24, or ≥25 cigarettes/d), and leisure-time physical activity, expressed as the sum of metabolic equivalents (MET) for each activity multiplied by the corresponding hours of such activity per week (none, <20, 20–39.9, or ≥40 MET-h/wk). Subjects were classified as having impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes, according the 1998 WHO diagnostic criteria (20). These 3 conditions combined were referred to in this paper to as the "glucose tolerance abnormality." Multiple logistic regression that included terms for the abovementioned variables was performed to estimate the odds ratio (OR) and 95% CI of each study outcome according to quartiles of scores for each dietary pattern, taking the lowest quartile group as the reference group. In the analysis of specific outcomes, i.e., impaired glucose tolerance, impaired fasting glucose, or diabetes, data for those with the other types of glucose tolerance abnormalities were excluded. Trend association was assessed by assigning a median score to each quartile for each dietary pattern. Analyses were repeated after stratification of known risk or preventive factors for diabetes including obesity, parental history of diabetes, smoking, and leisure-time physical activity. Statistical significance of the interactions between dietary pattern (as a continuous variable) and the stratified variables was assessed by the Wald χ^2 statistic. All analyses were done using SAS version 8.2 (21).

RESULTS

Factor loadings are equivalent to simple correlations between the food items and the dietary patterns. A positive loading indicates that the food item is positively associated with the dietary pattern, and a negative loading indicates an inverse association with the dietary pattern. The DFSA dietary pattern was characterized by frequent intake of fermented dairy products, milk, confectioneries, bread, fruits, and vegetables, and infrequent intake of shochu, a local alcoholic beverage in the study area (Table 1). The animal food dietary pattern was characterized by various kinds of animal foods, including red meat, poultry, seafood excluding fish, processed meat and fish products, and fried or broiled foods. The Japanese dietary pattern was characterized by foods traditionally consumed in Japan (soybean products, seaweeds, pickles, and green tea), vegetables, and fish. The proportion of the total variance explained by the 3 factors was 24%.

The 3 dietary patterns were related to some of the potential confounding variables and alcohol consumption (**Table 2**). Examinees at Kumamoto hospital had a higher score for the Japanese dietary pattern but lower scores for the DFSA and animal food dietary patterns than those at Fukuoka hospital. Men with a higher score for the DFSA dietary pattern engaged in higher levels of leisure-time physical activity and consumed smaller amounts of alcohol; in addition, they had a higher

[3] Abbreviations used: DASH, Dietary Approaches to Stop Hypertension; DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern); MET, metabolic equivalent; OR, odds ratio.

TABLE 1

Factor loading matrix for dietary patterns[1]

	DFSA dietary pattern	Animal food dietary pattern	Japanese dietary pattern
Fermented dairy products	0.61	—	—
Confectionary	0.55	0.18	—
Canned/dried fruits	0.52	—	—
Bread	0.47	—	−0.39
Fruits, not canned/dried	0.47	—	0.21
Fruits juice	0.47	—	—
Vegetable juice	0.41	—	0.17
Milk	0.40	—	—
Dressing oil	0.33	0.19	0.26
Soda, cola	0.30	0.20	−0.18
Shochu (alcoholic beverage)	−0.40	0.15	0.24
Red meat	—	0.68	—
Poultry	—	0.63	—
Fried foods	0.25	0.49	0.29
Broiled fish/broiled meat, all kinds	—	0.48	0.32
Seafood, except fish	—	0.47	0.18
Processed meat	0.17	0.46	—
Processed fish	—	0.41	0.18
Gyoza[2]	—	0.40	—
Liver	—	0.38	—
Egg	—	0.34	0.22
Noodle	—	0.34	—
Soybean products	—	—	0.64
Cooked vegetables	0.36	0.23	0.56
Seaweeds	0.27	—	0.55
Raw vegetables	0.45	—	0.52
Pickles	0.19	—	0.51
Green tea	—	−0.15	0.46
Fish	—	0.27	0.38
Potato	0.33	0.24	0.35
Garlic	0.20	—	0.32
Variance explained, %	8.5	7.9	7.7

[1] Factor loadings less than ± 0.15 were represented by a dash for simplicity; food items with factor loadings less than ± 0.30 for all dietary patterns (rice, mayonnaise, nuts, coffee, wine, beer, whisky, sake) were omitted.

[2] Dumpling with minced pork and vegetable stuffing.

proportion of nonsmokers than those with a lower score. Men with a higher score for the animal food dietary pattern had higher BMI and consumed larger amounts of alcohol. Men with a higher score for the Japanese dietary pattern engaged in higher levels of leisure-time physical activity, consumed greater amounts of alcohol, and had a higher proportion of nonsmokers than those with a lower score.

A total of 151, 384, and 112 men were identified as having impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes, respectively. The DFSA dietary pattern was significantly, inversely associated with glucose tolerance abnormalities, with men in the highest quartile of the dietary pattern having an OR that was half that of those in the lowest quartile (**Table 3**). The inverse association was consistent for impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes, although the pattern of decreasing trend differed somewhat among them. The Japanese dietary pattern showed a significant, positive trend association with impaired glucose tolerance (P for trend = 0.048); compared with the lowest quartile of the pattern, the OR for the upper 3 quartiles combined was 1.37 (95% CI = 1.03–1.82). No apparent trend association was observed for the animal food dietary pattern.

The association between the DFSA dietary pattern and glucose intolerance was further examined according to factors associated with type 2 diabetes (**Table 4**). Overall, the inverse association was consistent across subgroups stratified by the factors. However, some variations in the pattern of the association were observed; there was a large reduction in OR between the lowest (reference) and 2nd quartiles of the DFSA dietary pattern among individuals who had a larger body mass, whereas the OR gradually decreased as the dietary pattern score increased among those who had a normal body mass (P for interaction < 0.001). Such differences in patterns were also observed when the association was stratified by parental history of diabetes, although the interaction was not significant (P for interaction = 0.67).

DISCUSSION

We investigated the association between major dietary patterns and glucose tolerance status among middle-aged Japanese men. Of the 3 dietary patterns we identified, the DFSA dietary pattern had a significant, inverse association with glucose tolerance abnormalities or with each diagnostic subcategory. Additionally, the inverse association was consistent across subgroups stratified according to known factors predictive of diabetes.

Our study has several strengths. Glucose tolerance status was determined on the basis of an oral glucose tolerance test. Selection bias in terms of study participation was unlikely because of nonselective recruitment for the preretirement health

TABLE 2

Potential confounding variables and alcohol consumption by quartiles of dietary patterns in Japanese men

Dietary pattern	Hospital, % *Kumamoto*	Age, *mean y*	Rank, % *highest*	Parental history of diabetes, %	BMI, *mean kg/m²*	Smoking, *% current*	Leisure-time physical activity, *median MET-h/wk*	Alcohol,[1] *median mL/d*
DFSA dietary pattern								
Quartile 1 (low)	44	52.4	11	6	23.9	52	14.5	62
Quartile 2, 3	38	52.4	13	9	23.8	46	16	36
Quartile 4 (high)	31	52.4	18	12	23.7	44	16	14
P for trend[2]	<0.001	0.32	<0.001	<0.001	0.20	<0.01	0.02	<0.001
Animal food dietary pattern								
Quartile 1 (low)	42	52.4	15	8	23.6	48	16	22
Quartile 2, 3	38	52.4	14	9	23.8	48	16	39
Quartile 4 (high)	33	52.4	12	10	24.0	45	14	48
P for trend	<0.01	0.20	0.15	0.14	0.01	0.28	0.41	<0.001
Japanese dietary pattern								
Quartile 1 (low)30		52.4	18	9	23.8	52	10.5	23
Quartile 2, 3	39	52.4	13	8	23.8	46	16	43
Quartile 4 (high)	43	52.4	11	11	23.9	44	18	45
P for trend	<0.001	0.32	0.001	0.17	0.64	<0.01	<0.001	<0.001

1 Estimated from the consumption of 5 alcoholic beverages: beer, sake, shochu, wine, and whisky.
2 Mantel-Haenszel χ^2 test for categorical variables; linear regression analysis for continuous variables, assigning ordinal score to each category; leisure-time physical activity and alcohol consumption data were log-transformed.

examination and high study participation rate. The questionnaire was distributed and collected before the oral glucose tolerance test, and the data for subjects with a history of diabetes were excluded; thus, recall bias associated with glucose tolerance status was also unlikely. We controlled for major known or suspected confounding factors. Moreover, because the study participants were homogeneous in terms of occupation, sex, and age, the results were less likely to be biased by unknown or unmeasured confounding factors.

The present study also has some limitations. According to the validation study for the former version of the dietary questionnaire (14), including questions and response options similar to those of the current questionnaire, most nutrients and foods demonstrated fairly good correlation between the dietary record and the questionnaire; the correlation coefficients (r) of 0.80, 0.77, and 0.58 for bread, fruits, and dairy products, major food items of the DFSA dietary pattern, were relatively high. Therefore, bias associated with nondifferential misclassification in dietary assessment may be minimal for the analysis of the DFSA dietary pattern. On the other hand, the correlation between the dietary record and the questionnaire was moderate for meat ($r = 0.48$), poultry ($r = 0.59$), fish ($r = 0.51$), fermented soybean ($r = 0.52$), and vegetables ($r = 0.40$), and this may be a reason for the lack of an apparent association for the animal food or Japanese dietary patterns. Another issue regarding dietary assessment is that the calculation and

TABLE 3

OR of having glucose tolerance abnormality by quartiles of dietary patterns in Japanese men

Dietary pattern	Quartile							P for trend
		2		3		4 (high)		
	1 (low)	OR[2]	95%CI	OR	95%CI	OR	95%CI	
Glucose tolerance abnormality[1] (n = 647)								
DFSA dietary pattern	1.00	0.80	0.62–1.04	0.71	0.54–0.92	0.51	0.38–0.67	<0.0001
Animal food dietary pattern	1.00	1.15	0.88–1.51	0.89	0.67–1.16	0.97	0.74–1.27	0.43
Japanese dietary pattern	1.00	1.14	0.86–1.50	1.40	1.06–1.83	1.20	0.91–1.58	0.14
Impaired fasting glucose (n = 151)								
DFSA dietary pattern	1.00	1.00	0.63–1.59	0.94	0.59–1.50	0.54	0.32–0.91	0.02
Animal food dietary pattern	1.00	0.98	0.61–1.58	0.85	0.52–1.37	0.99	0.62–1.59	0.87
Japanese dietary pattern	1.00	0.98	0.59–1.60	1.28	0.79–2.06	0.90	0.54–1.49	0.85
Impaired glucose tolerance (n = 384)								
DFSA dietary pattern	1.00	0.70	0.51–0.96	0.62	0.45–0.85	0.50	0.36–0.70	<0.0001
Animal food dietary pattern	1.00	1.18	0.86–1.63	0.77	0.55–1.08	1.02	0.74–1.41	0.59
Japanese dietary pattern	1.00	1.25	0.89–1.75	1.50	1.07–2.10	1.39	0.99–1.94	0.048
Diabetes mellitus (n = 112)								
DFSA dietary pattern	1.00	0.92	0.54–1.55	0.71	0.41–1.22	0.50	0.28–0.91	0.01
Animal food dietary pattern	1.00	1.54	0.87–2.70	1.58	0.91–2.75	0.73	0.38–1.40	0.33
Japanese dietary pattern	1.00	1.03	0.59–1.80	1.27	0.73–2.20	0.96	0.54–1.69	1.00

1 Including impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus.
2 OR adjusted for hospital, age, occupational rank, parental history of diabetes, BMI, smoking, and leisure-time physical activity.

TABLE 4

OR of having glucose tolerance abnormality by quartiles of the DFSA dietary patterns, according to risk factor in Japanese men[1]

		Quartile								
			2		3		4 (high)			
	n	1 (low)	OR[2]	95%CI	OR	95%CI	OR	95%CI	*P* for trend
BMI									
<25 kg/m^2	1443	1.00	0.88	0.64–1.21	0.79	0.57–1.10	0.49	0.34–0.69	<0.0001
≥25 kg/m^2	663	1.00	0.64	0.41–0.99	0.58	0.38–0.91	0.55	0.35–0.86	0.01
Parental history of diabetes									
No	1917	1.00	0.83	0.63–1.09	0.77	0.58–1.01	0.50	0.37–0.68	<0.0001
Yes	189	1.00	0.45	0.17–1.21	0.26	0.01–0.70	0.37	0.14–0.93	0.06
Smoking									
No	1113	1.00	0.87	0.61–1.26	0.57	0.39–0.84	0.50	0.34–0.74	<0.0001
Yes	993	1.00	0.68	0.46–1.00	0.89	0.61–1.29	0.50	0.34–0.76	0.004
Leisure-time physical activity									
<20 MET-h/wk	1236	1.00	0.84	0.60–1.17	0.73	0.51–1.03	0.47	0.32–0.67	<0.0001
≥20 MET-h/wk	870	1.00	0.70	0.46–1.07	0.66	0.44–1.00	0.56	0.36–0.87	0.01

[1] Including impaired fasting plasma glucose, impaired glucose tolerance, and type 2 diabetes.
[2] OR adjusted for hospital, age, occupational rank, parental history of diabetes, BMI, smoking, and leisure-time physical activity.

validation of total energy and nutrient intakes from the present questionnaire have yet not been completed. Men with a high score on a dietary pattern likely consumed more energy than those with a low score; high energy intake usually increases the risk of type 2 diabetes, and the lack of adjustment for energy intake may cause a superfluous positive association. However, energy adjustment only strengthens, rather than diminishes the inverse association between DSFA dietary pattern and glucose tolerance abnormalities, the major finding of the present study. However, we cannot exclude the possibility that the positive trend association between the Japanese dietary pattern and impaired glucose tolerance was a result of confounding by energy intake.

Limitations of factor analysis arise from arbitrary decisions (7,8) involved in selecting and grouping foods for analysis from the questionnaire, in determining the number of factors to retain, in choosing the method of rotation of the initial factors to increase the interpretability of dietary patterns, and in labeling dietary patterns according to their factor loadings. Using factor analysis, Masaki et al. (22) identified a Western breakfast dietary pattern (similar to the DFSA pattern) and an animal dietary pattern in a cohort of men in Tokyo. Kim et al. (23) identified 3 major dietary patterns in a nationwide cohort in Japan: a healthy dietary pattern (similar to the DFSA pattern), a traditional dietary pattern (similar to the Japanese pattern), and a Western dietary pattern (similar to the animal food pattern). These findings suggest the existence of dietary patterns common to the Japanese. However, we also found important differences in loading patterns among these studies. For example, soybean products and seaweeds, which were the most closely correlated with the Japanese dietary pattern in our study, had the highest loadings with a healthy dietary pattern (similar to the DFSA pattern) in another study (23). Therefore, further exploratory studies are required to clarify dietary patterns among the Japanese before this approach is used.

The inverse association between the DFSA pattern and glucose tolerance abnormalities may represent beneficial effects of each food or nutrient contributing to the dietary pattern on glucose metabolism. Results of prospective studies (24–27) suggested that the intake of fruits and/or vegetables is inversely related to the risk of developing type 2 diabetes. Substancesrich in fruits and vegetables that were linked to a decreased risk of diabetes or insulin resistance include fiber (28), carotenoids (29), and magnesium (30). Milk consumption was strongly associated with a decreased risk of developing obesity and the insulin resistance syndrome (31), which are key risk factors for type 2 diabetes. Calcium reduces insulin resistance (32), but other substances in milk may also play a role. In addition to independent effects, there may be complex interactions among food factors constituting the DFSA dietary pattern. Note that the DFSA pattern is similar to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern (33) in that both are rich in fruits, vegetables, and dairy products, and that the DASH diet not only reduces blood pressure (33) but also improves insulin metabolism (34).

Both shochu and beer, 2 major alcohol beverages consumed by the study population, were inversely associated with the DFSA dietary pattern (**Appendix 2**), and men with the lowest quartile of the DFSA pattern score consumed considerably large amounts of alcohol (Table 2). Heavy drinking has been consistently related to increased diabetes risk, whereas moderate drinking may decrease the risk (35). The clear inverse gradient in alcohol consumption may thus account for the decreased odds of glucose tolerance abnormality among men with a higher score for the DFSA dietary pattern.

Confectionaries and soft drinks, which were positively related to the DFSA dietary pattern, may worsen the glucose metabolism due to the potentially detrimental effect of diets high in simple sugars on insulin sensitivity (36). However, epidemiologic evidence is conflicting (37,38). Furthermore, the effect of sugars on glycemic response is greatly attenuated when individuals consume >100 g of carbohydrates (39), as is the case for most Japanese (13) who eat rice as their staple food. Therefore, confectionaries and soft drinks may not play a large role in glucose metabolism in the study subjects. It would also be worth noting that not all food items associated with the DFSA pattern are necessarily causally related to outcome.

The Japanese dietary pattern was characterized by high consumption of traditional Japanese foods (soybean products, seaweeds, pickles, fish, and green tea) and vegetables. Because phytoestrogens in soy protein (40), polyphenols in green tea (41), and (n-3) PUFA rich in fish (42) are suggested to improve glucose metabolism, the Japanese dietary pattern may likely decrease the risk of type 2 diabetes. However, we found no such association; conversely, the Japanese dietary pattern showed a significant, positive association with impaired glucose tolerance. We have no ready reason for this outcome, but some nutritional characteristics of the Japanese diet (for instance, high in refined carbohydrate but low in protein) may adversely affect glucose metabolism beyond the aforementioned beneficial effects of Japanese foods.

Components of the animal food dietary pattern included meats and marine animal foods except fish. Higher scores of this pattern likely accompany greater consumption of fat, especially saturated fat, which may increase the risk of diabetes (42). Western studies (11,12) suggested that the Western dietary pattern, characterized by frequent red meat intake, confers a risk of type 2 diabetes. In the present study, however, the animal food dietary pattern was not apparently associated with an abnormality in glucose tolerance. The lack of an association may reflect moderate consumption of meat in the Japanese population; mean daily intake in men aged 40–49 y is ~100 g for total meat (13). In the subjects in this study, the mean weekly frequency of consumption was only 1.8 and 1.0 for red and processed meat, respectively (Appendix 2).

In conclusion, the present results indicate that a dietary pattern characterized by frequent consumption of dairy products, confectionaries, fruits, and vegetables but a low intake of local alcoholic beverages may be associated with a reduced risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes in Japanese men. Although our finding must be confirmed by prospective studies including women and individuals with various occupational backgrounds, an intervention to change dietary patterns may decrease type 2 diabetes risk in the Japanese population, whose consumption of dairy foods and fruits is currently low (43).

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APPENDIX 1

List of the combined food items

Food item	Foods or food groups combined
Seafood, except fish	Cuttlefish/octopus, shrimp/crab, oyster/shellfish
Soybean products	Miso soup, tofu, natto (fermented soybeans)
Pickles	Pickled ume, pickled scallion, pickled vegetables
Raw vegetables	Tomato, cucumber, cabbage, lettuce, Chinese radish/turnip, onion
Vegetable juice	Tomato juice, other juice
Heated vegetables	Carrot, pumpkin, onion, green pepper, spinach, leek
Seaweeds	Wakame, hijiki/konbu
Canned/dried fruits	Canned fruits, dried fruits
Fermented dairy products	Yogurt, cheese
Confectionary	Chocolate, caramel/candy, cake, Japanese cake, sweetened bun
Fried foods	Tempura/other deep-fried foods, fried foods
Broiled fish/broiled meat, all kinds	Broiled fish, broiled red meat, broiled chicken

APPENDIX 2

Intakes of selected dietary items according to quartile of dietary pattern score among Japanese men[1]

		DFSA dietary pattern			Animal food dietary pattern			Japanese dietary pattern		
Dietary item	All subjects	1 (low)	2, 3	4 (high)	1 (low)	2, 3	4 (high)	1 (low)	2, 3	4 (high)
						n/wk				
Red meat	1.8 ± 1.4	1.9 ± 1.5	1.7 ± 1.3	1.9 ± 1.6	0.7 ± 0.6	1.8 ± 1.1	3.0 ± 1.5	1.9 ± 1.5	1.8 ± 1.3	1.7 ± 1.4
Processed meat	1.0 ± 1.2	0.8 ± 1.0	1.0 ± 1.2	1.3 ± 1.4	0.5 ± 0.6	0.9 ± 1.0	1.8 ± 1.6	1.1 ± 1.3	1.0 ± 1.1	1.0 ± 1.3
Poultry	1.5 ± 1.2	1.6 ± 1.4	1.5 ± 1.2	1.5 ± 1.2	0.7 ± 0.5	1.4 ± 1.0	2.6 ± 1.3	1.4 ± 1.1	1.5 ± 1.2	1.7 ± 1.4
Fish	3.2 ± 1.9	3.5 ± 2.4	3.1 ± 1.8	3.2 ± 1.8	2.5 ± 1.7	3.2 ± 1.8	3.9 ± 2.1	2.3 ± 1.3	3.1 ± 1.8	4.2 ± 2.3
Seafood, except fish (3)[2]	2.3 ± 2.2	2.0 ± 2.0	2.2 ± 2.0	2.8 ± 2.5	1.3 ± 1.2	2.1 ± 1.7	3.8 ± 2.8	1.8 ± 1.5	2.4 ± 2.2	2.8 ± 2.4
Egg	3.4 ± 2.6	3.3 ± 2.4	3.3 ± 2.7	3.6 ± 2.6	2.3 ± 2.2	3.4 ± 2.3	4.5 ± 2.9	2.7 ± 2.2	3.3 ± 2.4	4.1 ± 3.0
Milk	3.8 ± 3.6	2.2 ± 2.3	3.6 ± 3.3	5.6 ± 4.4	3.7 ± 3.9	3.7 ± 3.6	3.9 ± 3.2	3.2 ± 3.4	3.8 ± 3.5	4.3 ± 3.9
Fermented dairy products (2)[2]	2.2 ± 2.7	0.8 ± 1.0	1.8 ± 1.9	4.3 ± 3.9	2.3 ± 3.4	2.1 ± 2.5	2.3 ± 2.4	2.0 ± 2.8	2.0 ± 2.3	2.8 ± 3.3
Fruits, not canned/dried	2.7 ± 2.6	1.4 ± 1.6	2.6 ± 2.2	4.4 ± 3.3	2.5 ± 2.8	2.8 ± 2.6	2.9 ± 2.5	2.1 ± 2.2	2.7 ± 2.5	3.5 ± 3.0
Raw vegetables (6)[2]	14.6 ± 9.4	10.8 ± 6.4	13.8 ± 7.7	20.0 ± 12.1	13.2 ± 10.0	14.2 ± 9.5	16.6 ± 8.1	9.6 ± 6.0	13.7 ± 6.9	21.4 ± 12.2
Cooked vegetables (6)[2]	10.0 ± 7.2	7.4 ± 5.7	9.7 ± 6.5	13.1 ± 8.7	8.2 ± 7.3	9.6 ± 7.2	12.4 ± 6.7	5.8 ± 3.9	9.0 ± 5.5	16.0 ± 8.8
Seaweeds (2)[2]	3.7 ± 3.2	2.8 ± 2.6	3.6 ± 3.2	4.7 ± 3.4	3.4 ± 3.4	3.5 ± 3.0	4.4 ± 3.2	1.8 ± 1.5	3.4 ± 2.6	6.2 ± 3.8
Soybean products (3)[2]	13.6 ± 7.2	13.4 ± 6.8	13.2 ± 6.9	14.7 ± 8.0	13.8 ± 8.0	13.2 ± 6.7	14.4 ± 7.1	8.4 ± 4.5	13.2 ± 5.1	19.7 ± 8.4
Pickles (3)[2]	8.2 ± 6.0	7.4 ± 5.9	7.8 ± 5.4	9.6 ± 6.8	7.9 ± 6.8	8.0 ± 5.8	8.8 ± 5.4	4.7 ± 3.5	7.8 ± 4.9	12.3 ± 7.3
Rice[3]	3.0 ± 1.0	3.1 ± 1.0	3.0 ± 1.0	2.8 ± 1.0	3.1 ± 1.0	2.9 ± 1.0	3.0 ± 1.0	2.6 ± 1.0	3.0 ± 0.9	3.2 ± 0.9
Bread	1.5 ± 2.2	0.5 ± 0.8	1.3 ± 1.8	3.0 ± 2.9	1.4 ± 2.3	1.6 ± 2.1	1.6 ± 2.2	3.0 ± 3.0	1.2 ± 1.6	0.8 ± 1.4
Confectionary (5)[2]	2.6 ± 3.2	0.9 ± 1.2	2.3 ± 2.3	5.1 ± 4.4	1.9 ± 2.7	2.6 ± 3.0	3.4 ± 3.7	3.1 ± 3.4	2.5 ± 3.1	2.4 ± 3.1
Green tea[4]	3.3 ± 2.4	3.6 ± 2.5	3.3 ± 2.3	3.3 ± 2.4	3.8 ± 2.5	3.3 ± 2.4	3.0 ± 2.2	2.0 ± 1.7	3.3 ± 2.1	4.8 ± 2.7
Shochu	3.0 ± 2.9	4.7 ± 2.7	2.8 ± 2.8	1.5 ± 2.3	2.3 ± 2.8	3.0 ± 2.9	3.5 ± 2.9	1.8 ± 2.6	3.2 ± 2.9	3.7 ± 2.9
Beer	3.0 ± 2.8	3.9 ± 2.8	2.9 ± 2.7	2.4 ± 2.6	1.7 ± 2.3	3.2 ± 2.7	3.9 ± 2.7	2.8 ± 2.8	3.2 ± 2.8	3.0 ± 2.8

1 Values are means ± SD.
2 Combined food items (number of foods or food groups combined).
3 Bowls/d.
4 Cups/d.

Physical activity and colorectal cancer: The Fukuoka Colorectal Cancer Study

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The number of cases of colorectal cancer in Japan has increased over the past few decades, and incidence rates are now among the highest in the world. The present investigation within the Fukuoka Colorectal Cancer Study, including 778 cases and 767 controls aged 20–74 years, examined the association between physical activity and colorectal cancer risk by subsite. Employment-associated and leisure time physical activity was assessed by a questionnaire and interview. Division of sites into the proximal and distal colon, as well as the rectum, revealed clear site-dependent protective effects, with adjustment for smoking, alcohol consumption, BMI and age. In males, greater job-related physical activity was associated with significant reduction of risk in the distal colon and rectum ($P = 0.047$ and 0.02, respectively), whereas total and moderate or hard non-job physical activity exerted effects limited to the rectum ($P = 0.01$ and 0.004, respectively). In females, job-related physical activity and moderate or hard non-job physical activity was also protective, but only in the distal colon. Separate assessment of the influence of BMI 10 years previous to the study showed increase in risk with obesity in males but not in females, limited to distal colon and rectum. The results of the present study indicate that physical activity associated with work and leisure-time exerts beneficial effects in Japanese, but not on the proximal colon. (*Cancer Sci* 2006; 97: 1099–1104)

Colorectal cancer is one of the most common cancers world-wide, accounting for approximately 10% of incident cases.[1] Both incidence and mortality have markedly increased over the past decades in Japan,[2] now among the countries with the highest rates of colorectal cancer in the world.[3] It has been argued that the change from low to high incidence is due to the adoption of a Westernized lifestyle, characterized by high intake of animal foods and low levels of physical exercise.[4] Many cohort and case-control studies have consistently shown that physical activity, as assessed by different methods, is associated with decreased risk of colorectal or colon cancer.[5,6] It is notable that a decreased risk associated with physical activity is more evident for colon cancer than colon and rectal cancer combined. In the case of rectal cancer, a protective association with physical activity has rarely been observed. According to a review published in 2002, two cohort studies and 10 case-control studies addressed the relationship between physical activity and rectal cancer, and only four case-control studies suggested a protective association.[5] An unsolved question is whether total energy expenditure or physical activity is more relevant to protection against colon cancer, and it is unsolved whether protective effects of physical activity might differ by the site of colon cancer. Several investigations have found a stronger protective association between physical activity and distal colon cancer than proximal colon lesions,[7–10] but others have noted a stronger risk reduction in the proximal segment,[11,12] or no difference.[13–16]

We therefore examined the relationship between physical activity at work, and during leisure time, commuting, housework, and shopping, and colorectal cancer risk in the Fukuoka Colorectal Cancer Study in Japan, with particular attention to the impact of physical activity on occurrence of cancer in the proximal colon, distal colon, and rectum. Because obesity has been reported to be associated with increased risk of colorectal cancer,[5] and is also closely associated with the level of physical activity, we also investigated the relationship between BMI and colorectal cancer development.

Materials and Methods

Details of methodological issues have been described elsewhere.[17] In brief, both cases and controls were residents of Fukuoka City and three adjacent areas. Cases were patients undergoing surgery for a first diagnosis of colorectal cancer at two university hospitals or six affiliated hospitals. Other eligibility criteria included the following characteristics: age of 20–74 years at the time of diagnosis; no prior history of partial or total removal of the colorectum, familial adenomatous polyposis, or inflammatory bowel disease; and mental and physical competence to give informed consent and to complete the interview. Of 1053 eligible cases, a total of 840 cases (80%) participated in the interview. Eligibility criteria for controls were the same as described for cases except for two items, that is, having no diagnosis of colorectal cancer and age of 20–74 years at the time of selection. A total of 1500 persons were selected as control candidates by two-stage random sampling. Fifteen small areas out of 178 in total were randomly selected, and approximately 100 persons were randomly selected in each small area. Numbers of control candidates by sex and 10-year age class were determined *a priori* in accordance with sex and age-specific numbers of incident cases of colorectal cancer in the Osaka Cancer Registry during the period 1988–1992.[18] A letter of invitation was sent to each candidate, and a telephone call was made if the candidate was listed in the telephone directory. At most three additional letters of invitation were mailed to non-respondents. A total of 833 persons (60%) participated in the survey.

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Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent; OR, odds ratio.

The cases were interviewed at each hospital during the period 2000–2003, and controls were surveyed during the period 2001–2002. Excluded from this analysis were 60 cases and 65 controls who had conditions that might have influenced their physical activities (prior history of angina pectoris, myocardial infarction, or cerebral infarction), and who were not perfectly independent in the activities of daily living. One control subject whose height was not measured and two cases whose cancers were both in colon and rectum were also excluded. Thus, 778 cases (456 men and 322 women) and 767 controls (470 men and 297 women) remained in the analysis.

Physical activity assessment. Questions on physical activities elicited information regarding the respondents' type of job, activities in commuting, housework, and shopping, and leisure-time activities at the time of 5 years prior to the interview. Five options were prepared to describe the type of job: sedentary or standing work (e.g., clerical work, taxi driving, housework); work with walking (e.g., delivery by walking, patrolling on foot), labor work (e.g., construction work, agricultural work, loads transport), hard labor work (e.g., digging or chopping with heavy tools, carrying heavy loads), and no job. Weekly minutes spent in walking, bicycling, and jogging were each ascertained regarding commuting, housework, and shopping on average in the year. Regular leisure-time activities were ascertained, on average over 1 year, with regularity defined as at least once per week. Information was obtained for up to three activities, in terms of the type of activity, numbers of months and of days per week that individuals participated in each activity, and minutes of participation per occasion.

Intensity of each non-job physical activity, including physical activity at leisure time, commuting, housework, and shopping, was classified into light, moderate, hard and very hard in terms of the MET on the basis of a published compilation for physical activity.[19] The time spent in non-job physical activity was multiplied by the corresponding MET value (light 2, moderate 4, hard 6 and very hard 8) to yield MET-hours per week of non-job activities. Twenty-eight subjects completed the questionnaire again after an interval of 1 year. The Spearman correlations for job-related and non-job physical activities were 0.67 and 0.57, respectively.

Job-related physical activities were categorized into three levels of sedentary (not employed, or sedentary or standing work), moderate (walking with work), and hard (labor work or hard labor work) for men. Because of the small number of female subjects engaged in jobs of moderate or hard activity, these two categories were combined into one. Non-job physical activity was categorized into three levels of 0, 0.1–15.9, or 16 + MET-hours per week, based on the distribution of physical activity among controls.

Anthropometric parameters. In this study, referent dates were the date of the onset of symptoms or screening for cases, and the date of interview for controls.

Participants reported height (cm) and body weight (kg) at the referent date and also body weight 10 years before the referent date. BMI, weight in kilograms divided by squared height in meters, was calculated as a measure of obesity at the referent date and 10 years before. Information on body weight 10 years before was missing with five cases and 11 controls, and their BMI 10 years before was based on the recent body weight. BMI was categorized into three groups of <23, 23–24.9, and 25+ kg/m^2, with reference to the results from a prospective study that examined the association between BMI and mortality in Japan.[20]

Other lifestyle parameters. To assess smoking habits, individuals were first asked whether they had ever smoked cigarettes every day for 1 year or longer. Then they were asked about the current status (before the symptoms or screening in the cases). For past smokers, their age when they started smoking, and that of quitting smoking, were ascertained. Years of smoking and numbers of cigarettes smoked per day were ascertained for each decade of age from the second to eighth decade.

Alcohol consumption at the time of 5 years prior to the referent dates was elicited, with alcohol use defined as drinking alcoholic beverages at least once per week over the period of 1 year or longer. Then individuals answered open-ended questions regarding the frequency of consumption (number of days per week) and the amount of alcohol consumed on the day of alcohol drinking, on average over a year at the time 5 years prior to the referent date. The amount of alcohol was expressed in conventional units: one go (180 mL) of sake, one large bottle (633 mL) of beer, and one half 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 a half unit.

Prior histories of medical conditions and surgeries were elicited, and activities of daily living were ascertained with classification into four categories (perfect independence, need of help for going outside, support needed at home, and bedridden).

Statistical analysis. In examining the association between physical activity and confounding factors, the Kruskal–Wallis test was used for continuous confounding variables, and the χ^2-test for dichotomous confounding variables. Association of physical activity and obesity with the risk of colorectal cancer was examined for men and women separately by use of multiple logistic regression analysis in terms of OR and 95% CI. Adjustment was made for age (<50, 50–54, 55–59, 60–64, 65–69, and 70+ years), cigarette smoking (0, 1–399, 400–799 and 800+ cigarette-years), alcohol use (0, 0.1–0.9, 1.0–1.9, or 2+ units per day), residential area (Fukuoka City or suburban area) and BMI 10 years before. Job-related physical activity and non-job physical activity were adjusted for each other. Statistical significance was concluded if the two-sided P-value was less than 0.05 or if 95% CI did not include unity. Those aged below 30 years were few (two cases and eight controls). Repeated analysis excluding these subjects did not change the results, and we presented the results based on the whole subjects. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Table 1 shows the association between several confounding factors and job-related physical activity among controls. In men, non-job physical activity was less among subjects whose job was physically hard than those who were sedentary at work. Sedentary men were older than those whose job was physically active. Such associations were not observed in women. In terms of non-job physical activity, the mean age was higher in both men and women with greater activity. None of the other confounding factors was related to level of non-job physical activity (Table 2).

Table 3 shows associations of physical activity with colon and rectal cancer risk in men. Hard work in terms of physical activity was associated with lower risks of both colon and rectal cancer as compared with sedentary work. A decrease in risk associated with job-related physical activity was noted for both distal and proximal colon cancer. Non-job physical activity was associated with a significantly decreased risk of only rectal cancer, although a similar tendency was noted for distal colon cancer. We also examined associations between moderate or hard non-job physical activity and colorectal cancer, and the results were similar to those for total non-job physical activity.

In women (Table 4), job-related physical activity was associated with a slightly decreased risk of colon cancer, and a significantly decreased risk of distal colon cancer, but not of rectal cancer. Similarly, total non-job physical activity was associated with a lower risk of colon cancer overall, and of distal colon cancer specifically, but not of either proximal colon or rectal cancer.

The current BMI was unrelated to either colon or rectal cancer in men and women (data not shown). BMI 10 years before was

Variable	Men				Women		
	Sedentary	Moderate	Hard	P*	Sedentary	Hard	P*
Number	290	75	105	NA	245	52	NA
Mean age (years)	59.2	56.4	57.8	0.03	58.1	58.1	0.57
Mean BMI (kg/m^2)	23.0	23.3	23.2	0.37	22.4	22.4	0.78
Mean MET-hours/week†	16.5	10.0	8.8	<0.0001	15.9	14.0	0.36
Alcohol user (%)‡	76.2	88.0	76.2	0.08	28.6	36.5	0.25
Heavy alcohol user (%)§	47.9	58.7	60.0	0.05	NS	NS	NS
Ever-smoker (%)¶	82.1	78.7	81.0	0.75	20.8	25.0	0.51
Heavy smoker (%)††	37.6	26.7	28.6	0.09	NS	NS	NS
Residents in Fukuoka City (%)	63.5	68.0	52.4	0.06	71.0	59.6	0.11

**P*-values (two-sided) were based on the Kruskal–Wallis test for continuous variables and χ^2-test for proportions. †Physical activity during leisure time, commuting, housework, and shopping. ‡Drinking alcohol at least once per week 5 years before. §Drinking alcohol at least 1.0 unit per day. Because of a small number of heavy drinkers in women (*n* = 19), only results for men are presented. ¶Smoking cigarettes daily for at least 1 year. ††Smoking at least 800 cigarette-years. Because of a small number of heavy smokers in women (*n* = 6), only results for men are presented. NA, not applicable; NS, result not significant.

Table 2. Characteristics of controls according to level of non-job physical activity† (MET-hours/week)

Variable	Men				Women			
	0	0.1–15.9	16.0+	P*	0	0.1–15.9	16.0+	P*
Number	161	151	158	NA	60	124	113	NA
Mean age (years)	57.5	57.7	60.2	0.03	55.2	57.7	60.2	0.0005
Mean BMI (kg/m^2)	23.2	23.0	23.2	0.30	22.5	22.2	22.6	0.52
Alcohol use (%)‡	75.2	82.8	76.6	0.23	23.3	30.7	32.7	0.43
Heavy alcohol use (%)§	52.2	57.0	48.1	0.30	NS	NS	NS	NS
Ever-smoker (%)¶	82.0	81.5	81.0	0.98	28.3	17.7	22.1	0.26
Heavy smoker (%)††	36.0	33.8	31.7	0.71	NS	NS	NS	NS
Residents in Fukuoka City (%)	57.1	64.2	63.9	0.34	61.7	69.4	72.6	0.33

**P*-values (two-sided) were based on the Kruskal–Wallis test for continuous variables and χ^2-test for proportions. †Physical activity during leisure time, commuting, housework, and shopping. ‡Drinking alcohol at least once per week 5 years before. §Drinking alcohol at least 1.0 unit per day. Because of a small number of heavy drinkers in women (*n* = 19), only results for men are presented. ¶Smoking cigarettes daily for at least 1 year. ††Smoking at least 800 cigarette-years. Because of a small number of heavy smokers in women (*n* = 6), only results for men are presented. NA, not applicable; NS, result not significant.

Table 3. Adjusted OR and 95% CI of colon and rectal cancer in relation to physical activity in men

	No. of controls	Colon		Proximal colon		Distal colon		Rectum	
		No.	OR (95% CI)†	No.	OR (95% CI)†	No.	OR (95% CI)†	No.	OR (95% CI)†
Job-related physical activity									
Sedentary	290	167	1.0 (referent)	56	1.0 (referent)	110	1.0 (referent)	138	1.0 (referent)
Moderate	75	37	0.9 (0.6–1.4)	16	1.2 (0.6–2.2)	21	0.8 (0.4–1.4)	33	0.9 (0.5–1.4)
Hard	105	44	0.7 (0.4–1.0)	16	0.7 (0.4–1.4)	28	0.6 (0.4–1.0)	37	0.6 (0.4–0.9)
Trend	NA	NA	*P* = 0.06	NA	*P* = 0.45	NA	*P* = 0.047	NA	*P* = 0.02
Total non-job physical activity‡									
0.0	161	87	1.0 (referent)	27	1.0 (referent)	60	1.0 (referent)	91	1.0 (referent)
0.1–15.9	151	83	0.9 (0.6–1.4)	33	1.2 (0.6–2.1)	49	0.8 (0.5–1.3)	61	0.6 (0.4–0.9)
16.0+	158	78	0.8 (0.5–1.2)	28	0.9 (0.5–1.7)	50	0.7 (0.4–1.1)	56	0.5 (0.3–0.8)
Trend	NA	NA	*P* = 0.22	NA	*P* = 0.69	NA	*P* = 0.19	NA	*P* = 0.01
Moderate or hard non-job physical activity‡									
0.0	184	105	1.0 (referent)	31	1.0 (referent)	74	1.0 (referent)	104	1.0 (referent)
0.1–14.9	137	68	0.8 (0.6–1.2)	29	1.1 (0.6–2.1)	38	0.7 (0.4–1.1)	53	0.6 (0.4–0.9)
15.0+	149	75	0.8 (0.5–1.1)	28	1.0 (0.6–1.8)	47	0.7 (0.4–1.0)	51	0.5 (0.3–0.8)
Trend	NA	NA	*P* = 0.24	NA	*P* = 0.99	NA	*P* = 0.12	NA	*P* = 0.004

†Adjustment was made for age, cigarette smoking, alcohol use, residential area, BMI of 10 years before, and non-job physical activities or job-related activities. ‡MET-hours/week. Physical activities during leisure time, commuting, housework, and shopping. NA, not applicable.

	No. of controls	Colon		Proximal colon		Distal colon		Rectum	
		No.	OR (95% CI)†	No.	OR (95% CI)†	No.	OR (95% CI)†	No.	OR (95% CI)†
Job-related physical activity									
Sedentary	245	166	1.0 (referent)	72	1.0 (referent)	94	1.0 (referent)	107	1.0 (referent)
Active	52	24	0.7 (0.4–1.2)	15	1.2 (0.6–2.3)	9	0.4 (0.2–0.8)	25	1.1 (0.6–1.9)
Trend	NA	NA	$P = 0.18$	NA	$P = 0.65$	NA	$P = 0.02$	NA	$P = 0.81$
Total non-job physical activity‡									
0.0	60	41	1.0 (referent)	11	1.0 (referent)	30	1.0 (referent)	26	1.0 (referent)
0.1–15.9	124	78	0.9 (0.5–1.5)	37	1.5 (0.7–3.3)	41	0.7 (0.4–1.3)	61	1.2 (0.7–2.3)
16.0+	113	71	0.8 (0.5–1.4)	39	1.6 (0.7–3.6)	32	0.6 (0.3–1.1)	45	0.9 (0.5–1.8)
Trend	NA	NA	$P = 0.45$	NA	$P = 0.41$	NA	$P = 0.12$	NA	$P = 0.47$
Moderate or hard non-job physical activity‡									
0	69	47	1.0 (referent)	15	1.0 (referent)	32	1.0 (referent)	30	1.0 (referent)
0.1–14.9	121	81	1.0 (0.6–1.6)	37	1.3 (0.6–2.5)	44	0.8 (0.5–1.5)	62	1.3 (0.7–2.2)
15.0+	107	62	0.8 (0.5–1.4)	35	1.3 (0.6–2.7)	27	0.5 (0.3–1.1)	40	0.9 (0.5–1.7)
Trend	NA	NA	$P = 0.35$	NA	$P = 0.59$	NA	$P = 0.09$	NA	$P = 0.41$

†Adjustment was made for age, cigarette smoking, alcohol use, residential area, BMI of 10 years before, and non-job physical activities or job-related activities. ‡MET-hours/week. Physical activities at leisure time, commuting, housework, and shopping. NA, not applicable.

Table 5. Adjusted OR and 95% CI of colon and rectal cancer in relation to BMI of 10 years before in men and women

	No. of controls	Colon		Proximal colon		Distal colon		Rectum	
		No.	OR (95% CI)†	No.	OR (95% CI)†	No.	OR (95% CI)†	No.	OR (95% CI)†
BMI‡ of 10 years before									
Men									
<23.0	237	96	1.0 (referent)	39	1.0 (referent)	56	1.0 (referent)	91	1.0 (referent)
23.0–24.9	118	68	1.3 (0.9–2.0)	26	1.3 (0.8–2.3)	42	1.4 (0.9–2.3)	51	1.1 (0.7–1.7)
25.0+	115	84	1.7 (1.2–2.5)	23	1.2 (0.7–2.1)	61	2.1 (1.4–3.3)	66	1.5 (1.0–2.3)
Trend	NA	NA	$P = 0.0063$	NA	$P = 0.49$	NA	$P = 0.0009$	NA	$P = 0.049$
Women									
<23.0	182	120	1.0 (referent)	52	1.0 (referent)	68	1.0 (referent)	75	1.0 (referent)
23.0–24.9	56	32	0.8 (0.5–1.3)	17	0.9 (0.5–1.8)	15	0.7 (0.3–1.3)	29	1.5 (0.8–2.7)
25.0+	59	38	0.9 (0.5–1.4)	18	0.8 (0.4–1.6)	20	0.9 (0.5–1.6)	28	1.2 (0.7–2.1)
Trend	NA	NA	$P = 0.45$	NA	$P = 0.51$	NA	$P = 0.58$	NA	$P = 0.53$

†Adjustment was made for age, cigarette smoking, alcohol use, residential area, and physical activity. ‡kg/m². NA, not applicable.

associated with a significant increase in the risk of colon and rectal cancer in men. Increased risk associated with obesity was noted almost exclusively for distal colon cancer. However, there was no such association in women (Table 5).

Discussion

The present study adds to evidence that physical activity confers decreased risk of colon cancer, especially of distal colon cancer in both men and women. A notable finding in the present study was that physical activity was also protective against rectal cancer in men exclusively. Obesity was also related to increased risks of distal colon and rectal cancer in men only.

Most previous epidemiological studies have suggested physical activity reduces colon cancer risk independent of race, society, and sex, whereas associations of physical activity with rectal cancer risk have been inconsistent. At least 12 case-control studies[10,11,13–16,21–26] and three cohort studies[12,27,28] have examined the relationship between physical activity and rectal cancer risk. Some case-control studies found a decreased risk associated with occupational physical activity in men and women combined[11] and in men,[23] with leisure-time physical activity in men not in women,[13] and with total physical activity in both men and women.[22,25] Other case-control studies failed to find a protective association with physical activity assessed differently in men and women,[15,26] in men and women combined[21] and in men.[10,14,16,24] Colbert *et al.* observed a substantial decrease in the risk of rectal cancer associated with physically moderate to heavy work in a cohort study of male smokers,[28] but no association was observed between occupational activity and rectal cancer in either men or women,[12] and in men[27] in two other cohort studies. We have no clear explanation to our finding that physical activity was protective against rectal cancer only in men. The observed gender difference might have been due to chance. In the present study, both occupational activity and non-job physical activity were associated with reduced risk of rectal cancer in men, adding to evidence that physical activity is protective against rectal cancer.

As reviewed elsewhere, the suggested mechanisms of risk reduction of colon cancer by physical activity include shortening the bowel intestinal transit time, enhancing immune function, increasing prostaglandin F and decreasing prostaglandin E2, maintenance of insulin sensitivity, lowering activity of insulin-like growth factor, sex hormones and bile acid secretion, and decreasing adiposity.[5,29–31] However, it is unclear which mechanisms are important for colorectal cancer prevention. Taking the available information on site-specific influence into account,[32] our present results might provide some clarification, as the effects were limited to the distal colon and rectum. Hyperinsulinemia and type 2 diabetes mellitus have been shown to be associated with increased risk of proximal colon cancer rather than distal segment,[33,34] and the possibility of physical activity impacting on insulin levels does not appear to be a likely mechanism to explain our findings. However, our results for BMI are of great interest and difficult to explain.

Given the fact that the distal colon mainly functions in fecal storage, it could be that the characteristics of feces and their passage is most important. Constipation is a possible risk factor of colon cancer,[35–38] and this can be relieved by exercise.[39–42] High physical activity has been reported to be related to low prevalence of constipation in some,[43,44] but not all, studies.[45] One possibility that deserves further consideration is that there could be an association between exercise and sunlight, and therefore vitamin D levels, thought to be protective against neoplasia in the colon and rectum.[46–48]

Several previous studies suggested that more vigorous exercise had a stronger association with risk reduction than light or moderate activity.[9,25,49] The most frequent activities among participants in the present study were walking, gardening, and golf, these being light or moderate in intensity. In addition, more than half of participants reported that they never engaged in moderate or hard activities at leisure time. The observed decrease in the risk with moderate or hard activity was not greater than that with total activity.

Obesity has been shown to be associated with increased risk of colon cancer, but the association seems to be weaker and less consistent in women than in men.[5] Although reasons for the gender difference in risk have not been clarified, estrogen might be an explanation. Several observational studies reported a reduced risk of colon cancer associated with hormone replacement therapy.[50–52] It has also been observed that obesity is not associated with increased risk of colon cancer in postmenopausal women in several observational studies.[53–55] Increased estrogen levels related to obesity, particularly in postmenopausal women, probably confer reduction in the risk linked with obesity. Again, the present study showed the gender difference in the association between obesity and rectal cancer. This finding is in agreement with the previous observations in case-control studies in Sweden[56] and in Hawaii.[13]

The present case-control study has advantages of being a population-based study with an adequate number of participants, who were all interviewed about all types of physical activity, with attention to the job setting and calculation of energy expenditure. However, there were several limitations that should be noted. The first is that we did not directly validate the method of assessing physical activities, although the measurement was highly reproducible. Another limitation concerned the referent period as to physical activity. In the present study, physical activity only in the recent past was ascertained. Long-term, habitual physical exercise at work or leisure has been suggested to be more protective.[57,58] Dietary factors such as vegetables and red meat, which seem to modify the risk of colorectal cancer, were not taken into account in the present study. We actually carried out a dietary survey in the Fukuoka Colorectal Cancer Study, but validation of the dietary assessment was not completed. It is unlikely that the observed associations with physical activity and obesity were due to the uncontrolled confounding effect of dietary factors. Reduced risk of colon or colorectal cancer associated with physical activity has been observed regardless of adjustment for dietary factors in many studies.[9,11,13,15,21,24,25]

Despite some inconsistencies with earlier studies, the present investigation suggests that physical activity and weight control are important for prevention of cancer in the distal colon and rectum, especially in males.

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