RESEARCH COMMUNICATION

Lack of Influence of the *ADH1B Arg47His* Genetic Polymorphism on Risk of Colorectal Adenoma in Middle-aged Japanese Men

Guang Yin[1*], Nobuyuki Hamajima[1], Makiko Morita[2], Osamu Tajima[3], Shinji Tabata[4], Suminori Kono[5]

Abstract

Alcohol consumption is one of the risk factors for colorectal cancers and adenomas. Since alcohol dehydrogenase is a key enzyme in alcohol metabolism, it may thus play a role in colorectal carcinogenesis. The present study was conducted to asess the association of a functional *ADH1B Arg47His* polymorphism with colorectal adenomas in a case-control study of male officials in the Self-Defense Forces who received a pre-retirement health examination at two Self-Defense Forces hospitals. The study subjects comprised 455 with colorectal adenomas and 1,052 controls without polyps, all of whom underwent total colonoscopy. Statistical adjustment was made for age, hospital, Self-Defense Forces rank, body mass index, cigarette-years, and alcohol consumption. There was no measurable association between the *ADH1B Arg47His* polymorphism and colorectal adenoma development. The adjusted odds ratio for individuals with the *47His/His* genotype compared to those with individuals with *47Arg* alleles was 1.18 (95% confidence interval 0.94-1.49). There was no influence of the level of alcohol consumption (interaction *P* = 0.84). In addition, there were no clear interactions of the *ADH1B* with *ALDH2 Glu487Lys* and *MTHFR C677T* with regard to the risk of colorectal adenoma. In conclusion, the present study suggested that the *ADH1B Arg47His* polymorphism does not contribute to the risk of colorectal adenoma in any subgroup of middle-aged Japanese men defined by alcohol drinking, as well as the *ALDH2 Glu487Lys* and *MTHFR C677T* genotypes.

Keywords: Colorectal adenomas - ADH1B polymorphism - alcohol use - gene-environment interaction - case-control study

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Introduction

Alcohol consumption is a conclusive risk factor of colorectal adenocarcinoma among men (WCRF/AICR, 2007). The increased risk might be caused by acetaldehyde, the first metabolite in ethanol catabolism, which has a carcinogenic effect in animals (Seitz et al., 1990; Feron et al., 1991) and in humans (Seitz et al., 1996). Additionally, the effects of alcohol may be mediated through the low folate concentration in blood, because alcohol and acetaldehyde disturb the absorption of folate (Giovannucci, 2004).

Ethanol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH), and further metabolized to acetate by aldehyde dehydrogenase (ALDH). Human ADH has several isoenzymes, whose functional polymorphisms are known for *ADH1B* and *ADH1C* genes (Yoshida et al., 1991). *ADH1B Arg47His* polymorphism (rs1229984) affects the enzyme activity substantially; the *47His* (alternatively *ADH2*2*) is an allele with faster ethanol oxidation. *ADH1C Ile349Val* polymorphism (rs698) also influences the ADH activity to a lesser extent; the *349Ile* (alternatively *ADH3*1*) is an allele with moderately faster oxidation (Bosron and Li, 1986). The *ADH1B 47His* allele is the major allele in Asians, while it is very rarely in Caucasian populations. On the contrast, the *ADH1C 349Val* allele is rare in Asians, while fairly common in Caucasians (Osier et al., 2002; Brennan et al., 2004). ALDH2 encoding mitochondrial ALDH contributes to acetaldehyde oxidation in human liver, which has a polymorphism of *Glu487Lys* (rs671). The variant, *487Lys* allele (alternatively *ALDH2*2*), results in an inactive form, which is found almost exclusively in Asian populations (Takeshita et al., 1994; Brennan et al., 2004).

Several studies have investigated the association between the *ADH1B* genotype and colorectal cancer risk. *ADH1B 47Arg* allele was associated with a moderate increase in the risk, when compared with the *His/His* genotype in Japan (Matsuo et al., 2006; Yin et al., 2007), but not in Spain (Landi et al., 2005). To our knowledge, no studies have examined the role of *ADH1B Arg47His* polymorphism on colorectal adenoma risk. Meanwhile,

*[1]Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, [2]Department of Molecular Biology, University of Occupational and Environmental Health, Yahatanishi-ku, Kitakyushu, [3]Self-Defense Forces Kumamoto Hospital, Kumamoto, [4]Self-Defense Forces Fukuoka Hospital, Kasuga, [5]Department of Preventive Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan *For correspondence: yinguang@med.nagoya-u.ac.jp*

three studies have examined the association between the *ADH1C Ile349Val* polymorphism and colorectal adenomas in Caucasians, producing inconsistent results (Giovannucci et al., 2003; Tiemersma et al., 2003; Jung et al., 2008). Although there was no difference in the distribution of *ADH1C* genotype between adenoma cases and controls as a whole in these studies, inconsistent associations were observed among drinkers. One study showed an increased risk of adenoma for those with the *ADH1C 349Ile/Ile* genotype when alcohol consumption was high (Tiemersma et al., 2003), whereas two other studies reported that the increased risk of adenoma was associated with *ADH1C 349Val* allele for men with high alcohol consumption (Giovannucci et al., 2003; Jung et al., 2008). Several studies of the *ALDH2* polymorphism and colorectal cancer or adenomas have been done in Japan (Yokoyama et al., 1998; Murata et al., 1999; Matsuo et al., 2002; Hirose et al., 2005; Matsuo et al., 2006; Yin et al., 2007). An approximately 3-fold increase in the risk of colorectal cancer was observed for the *ALDH2 487Glu/Lys* genotype versus the *ALDH2 487Glu/Glu* genotype among alcoholics (Yokoyama et al., 1998). Another study suggested that an increase in the risk of colon cancer, not of rectal cancer, was associated with high alcohol consumption among individuals with the *ALDH2 487Glu/Lys* genotype (Murata et al., 1999). A small case-control study showed a positive interaction between high alcohol consumption and the *ALDH2 487Glu/Lys* genotype, particularly for the risk of rectal cancer (Matsuo et al., 2002). In contrast, the *ALDH2* polymorphism did not show any measurable association with colorectal cancer (Matsuo et al., 2006; Yin et al., 2007) or adenomas (Hirose et al., 2005).

Methylenetetrahydrofolate redutase (MTHFR) is a key enzyme in folate metabolism. The *MTHFR C677T* (rs1801133) is a functional polymorphism in exon 4, resulting in an alanine to valine substitution at codon 222, and the *677TT* genotype has no more than 30% of normal enzyme activity (Frosst et al., 1995). A meta-analysis reported that decreased risk of colorectal cancer associated with the *MTHFR 677TT* genotype has consistently been observed with either high or low level of folate. Meanwhile, in the colorectal adenoma, the *MTHFR 677TT* genotype seems to be associated with increased risk, when folate status in low (Kono and Chen, 2005).

The present study examined the association of the *ADH1B Arg47His* polymorphism with colorectal adenomas in a case-control study of middle-aged Japanese men, focusing on gene-environment interactions. Our previous study reported an association between the *ALDH2 Glu487Lys* or *MTHFR C677T* polymorphism and risk of colorectal adenomas in this population (Hirose et al., 2005). Thus, we analyzed the effect of gene-gene interactions between *ADH1B* and *ALDH2* polymorphisms and between *ADH1B* and *MTHFR* polymorphisms on the risk of colorectal adenomas.

Materials and Methods

Subjects

Study subjects were male officials in the Self-Defense Forces (SDF) who received a pre-retirement health examination at the SDF Fukuoka Hospital (Kasuga, Japan) or Kumamoto Hospital (Kumamoto, Japan) during the period from January 1997 to March 2001. The pre-retirement health examination is a nationwide program offered by the SDF. Details of the health examination have been described elsewhere (Hirose et al., 2005; Ueda et al., 2008). In addition to blood samples for routine use in the health examination, a sample of 7 mL fasting venous blood was obtained for the purpose of medical research. The study was approved by the ethics committee of the Faculty of Medical Science, Kyushu University. All subjects gave written informed consent prior to their participation in the study.

The present study included 455 individuals with histologically confirmed colorectal adenoma and 1,052 individuals (controls) without polyps, all of whom underwent total colonoscopies. In the consecutive series of 2,459 men aged 46-59 years, 5 men refused to participate in the survey, and another 77 men did not receive a colonoscopy. Furthermore, 242 men were excluded from the study because of a prior history of colectomy ($n = 17$), colorectal polypectomy ($n = 212$), malignant neoplasm ($n = 27$), or inflammatory bowel disease ($n = 1$); some of the men had two or more reasons for exclusion. In the remaining 2,135 men, colonoscopic findings were classified as colorectal cancer ($n = 1$), polyp ($n = 938$), non-polyp benign lesion such as diverticula ($n = 123$), and normal ($n = 1,073$). Of the 938 with colorectal polyps, 461 were found to have adenoma without in situ or invasive carcinoma. Of the 1,196 with normal colonoscopy or non-polyp benign lesions, 1,067 underwent total colonoscopy and were used as controls. Finally, 21 men (6 cases and 15 controls) were excluded due to lack of DNA samples, leaving a total of 455 cases and 1,052 controls for analysis.

The proximal colon included the cecum, ascending colon, and transverse colon. The numbers of cases having adenomas at the proximal colon alone, the distal colon and/or rectum alone, and both proximal and distal segments were 149, 239, and 67, respectively. Distal colon adenomas and rectal adenomas were combined because cases with rectal adenomas alone were few ($n = 42$).

Lifestyle questionnaire

A self-administered questionnaire was used to ascertain SDF rank, body weight, height, alcohol use, smoking habits, and other lifestyle characteristics. The SDF rank was classified as "low", "middle", or "high". Body mass index (BMI) was calculated by dividing weight in kilograms by squared height in meters and was categorized into four levels using quartiles in the distribution of the control group. Alcohol drinkers were defined as those who drank once a week or more over a period of 1 year or longer. Past drinkers were separated from life-long nondrinkers. Current drinkers were asked about frequency and amount of consumption per occasion of five different alcoholic beverages (sake, shochu, beer, whisky/brandy, and wine) on average in the past year, and their daily intake of ethanol was estimated. Alcohol consumption was classified as "never", "past use", or "current use", and the "current use" group was further

subdivided by consumption of <30, 30-59, or ≥60 mL ethanol per day. Smokers were defined as those who had ever smoked cigarettes daily for at least 1 year. Both current and past smokers were asked about the average number of cigarettes smoked per day and total years of smoking. Cumulative exposure to cigarette smoking was expressed as cigarette-years, which were calculated by multiplying the average number of cigarettes per day by the total years of smoking. Cigarette smoking was classified into 0, 1-399, 400-799, and ≥800 cigarette-years.

Genotyping

DNA was extracted from the buffy coat using a commercial kit (QIAGEN GmbH, Hilden, Germany), and genotyping was performed with a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The PCR was performed in a reaction mixture of 10 μL containing 0.5 units of Taq polymerase and 1 μL of template DNA at a concentration of approximately 50-150 ng/μL. The *ADH1B Arg47His* genotypes were determined according to the previous method (Osier et al., 2002). Primers for *ADH1B Arg47His* genotypes were 5'-att cta aat tgt tta att caa gaa g-3' (sense) and 5'-act aac aca gaa tta ctg gac-3' (antisense). PCR products were digested with 20 units of *MslI* for 16 hours at 37 °C in a mixture of 20 μL, resulting in fragments of 443 bp and 242 bp for the *47His* allele and 685 bp for the *47Arg* allele. The digested PCR products were separated by electrophoresis on 3% agarose gels (NuiSieve GTG) and visualized with ethidium bromide. The *ALDH2 Glu487Lys* genotype and the *MTHFR C677T* genotype were determined as described by our previous study (Hirose et al., 2005).

Statistical analysis

The associations of the genetic polymorphisms with risk of colorectal adenomas were examined by multiple logistic regression analysis including indicator variables for age (continuous variable), hospital (Fukuoka Hospital and Kumamoto Hospital), SDF rank (low, middle, or high), BMI (categorized into four levels using quartiles in the distribution in the control group), cigarette-years (0, 1-399, 400-799, and ≥800), and alcohol intake (never, past use, or current use with consumption of <30, 30-59, or ≥60 mL/day) as covariates. Adjusted odds ratio (OR) and 95% confidence interval (CI) were obtained from the logistic regression coefficient and the standard error for the corresponding indicator variable. Statistical significance for the interaction was tested by the likelihood ratio test comparing the logistic models with and without interaction terms for the genotype and alcohol category. Statistical significance was concluded if the two-sided P-value was less than 0.05, or if the 95% CI did not include unity. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

High consumption of alcohol was associated with a moderate increase in the risk of colorectal adenoma. Adjusted OR (95% CI) of colorectal adenomas for life-long non-drinkers, past drinkers, and current drinkers consuming <30, 30-59, or ≥60 mL alcohol per day were 1 (reference), 1.07 (0.52-2.23), 0.87 (0.58-1.30), 1.46 (1.00-2.14), and 1.54 (1.04-2.27), respectively, when the genetic polymorphisms were not taken into account.

Among the controls, the frequencies of the *His/His*, *Arg/His*, and *Arg/Arg* genotypes of the *ADH1B Arg47His* polymorphism were 55.9%, 37.4%, and 6.7%, respectively (Table 1). The frequencies of the *ALDH2 Glu487Lys* genotypes and *MTHFR C677T* genotypes were reported by our previous study (Hirose et al., 2005). The distribution of genotypes for the *ADH1B Arg47His* polymorphism was in agreement with the Hardy-Weinberg equilibrium in both cases and controls. There was no measurable association between the *ADH1B Arg47His* polymorphism and colorectal adenoma. The adjusted OR for individuals with the *47His/His* genotype compared to those with individuals with *47Arg* allele was 1.18 (95% CI 0.94-1.49). However, the individuals with the *ADH1B 47His/His* genotype was significantly associated with the increased risk for distal and rectum adenomas, but not for proximal adenomas. The adjusted OR for individuals with the *ADH1B 47His/His* compared to those without was 1.38 (95% CI 1.02-1.85) in distal colon and rectal adenomas.

Table 2 summarizes the results from the analysis of the interaction between alcohol intake and the *ADH1B Arg47His* polymorphism for the risk of colorectal adenoma by site. In this analysis, individuals heterozygous for the *ADH1B* polymorphism were combined with those homozygous for the minor allele, and past alcohol drinkers were excluded. There was no appreciable effect modification of the *ADH1B* polymorphism on the association between alcohol consumption and colorectal adenomas (interaction $P = 0.84$). However, individuals with *47His/His* genotype was associated with the increased risk of colorectal adenoma compared to those with *47Arg* allele among <30 mL/day drinkers (OR, 1.80; 95% CI,

Table 1. Adjusted Odds Ratio (OR) and 95% Confidence Interval (95% CI) of *ADH1B Arg47His* for Colorectal Adenomas by Site

Genotype‡	Controls	Colorectum		Proximal colon		Distal colon and rectum	
	No. (%)	No. (%)	OR (95% CI)†	No. (%)	OR (95% CI)†	No. (%)	OR (95% CI)†
His/His	588 (55.9)	268 (59.0)	1 (Reference)	79 (53.0)	1 (Reference)	148 (62.2)	1 (Reference)
Arg/His	393 (37.4)	161 (35.5)	0.86 (0.68-1.09)	60 (40.3)	1.12 (0.78-1.62)	76 (31.9)	0.72 (0.53-0.99)
Arg/Arg	71 (6.7)	25 (5.5)	0.75 (0.46-1.23)	10 (6.7)	1.09 (0.54-2.23)	14 (5.9)	0.73 (0.40-1.36)
Arg/His + Arg/Arg	464 (44.1)	186 (41.0)	1 (Reference)	70 (47.0)	1 (Reference)	90 (37.8)	1 (Reference)
His/His	588 (55.9)	268 (59.0)	1.18 (0.94-1.49)	79 (53.0)	0.89 (0.63-1.27)	148 (62.2)	1.38 (1.02-1.85)

†Adjusted for age, hospital, Self-Defense Forces rank, body mass index, cigarette smoking, and alcohol use; ‡One case was excluded because of undetermined genotype of *ADH1B Arg47His*.

Table 2. Adjusted Odds Ratio (OR) and 95% Confidence Interval (95% CI) of *ADH1B Arg47His* for Colorectal Adenomas by Alcohol Use and Site

Genotype		Alcohol intake (mL/day)				Interaction
		Never use	<30	30-59	≥60	
Colorectum						
Arg/His + Arg/Arg	No.†	24/61	27/132	68/135	63/120	P = 0.84
	OR (95% CI)‡	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	
His/His	No.†	27/84	69/191	86/167	77/129	
	OR (95% CI)‡	0.77 (0.40-1.51)	1.80 (1.08-3.00)	0.99 (0.66-1.50)	1.31 (0.85-2.02)	
Proximal colon						
Arg/His + Arg/Arg	No.†	11/61	12/132	24/135	21/120	P = 0.72
	OR (95% CI)‡	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	
His/His	No.†	11/84	22/191	18/167	25/129	
	OR (95% CI)‡	0.72 (0.28-1.87)	1.32 (0.61-2.84)	0.54 (0.27-1.09)	1.24 (0.64-2.38)	
Distal colon and rectum						
Arg/His + Arg/Arg	No.†	10/61	11/132	34/135	33/120	P = 0.79
	OR (95% CI)‡	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	
His/His	No.†	14/84	36/191	52/167	41/129	
	OR (95% CI)‡	1.01 (0.40-2.57)	2.43 (1.17-5.03)	1.23 (0.73-2.05)	1.44 (0.83-2.51)	

†Numbers of cases/controls; ‡Adjusted for age, hospital, Self-Defense Forces rank, body mass index, and cigarette smoking.

Table 3. Adjusted Odds Ratio (OR) and 95% Confidence Interval (95% CI) of *ADH1B Arg47His* for Colorectal Adenoma by *ALDH2 Glu487Lys* and Site

Genotype	ALDH2 487Glu/Glu		ALDH2 487Glu/Lys + Lys/Lys		Interaction
	No.†	OR (95% CI)‡	No.†	OR (95% CI)‡	
Colorectum					
Arg/His + Arg/Arg	123/270	1 (Reference)	62/192	1 (Reference)	P = 0.79
His/His	177/335	1.21 (0.90-1.61)	91/252	1.10 (0.75-1.62)	
Proximal colon adenomas					
Arg/His + Arg/Arg	43/270	1 (Reference)	27/192	1 (Reference)	P = 0.41
His/His	52/335	1.01 (0.65-1.57)	27/252	0.72 (0.40-1.29)	
Distal colon and rectal adenomas					
Arg/His + Arg/Arg	60/270	1 (Reference)	30/192	1 (Reference)	P = 0.83
His/His	94/335	1.35 (0.93-1.95)	54/252	1.39 (0.85-2.28)	

†Numbers of cases/controls; ‡Adjusted for age, hospital, Self-Defense Forces rank, body mass index, cigarette smoking.

Table 4. Adjusted Odds Ratio (OR) and 95% Confidence Interval (95% CI) of *ADH1B Arg47His* for Colorectal Adenoma by *MTHFR C677T* and Site

Genotype	MTHFR 677CC		MTHFR 677CT + TT		Interaction
	No.†	OR (95% CI)‡	No.†	OR (95% CI)‡	
Colorectum					
Arg/His + Arg/Arg	72/178	1 (Reference)	113/284	1 (Reference)	P = 0.85
His/His	109/220	1.22 (0.84-1.77)	158/368	1.13 (0.84-1.52)	
Proximal colon adenomas					
Arg/His + Arg/Arg	27/178	1 (Reference)	43/284	1 (Reference)	P = 0.93
His/His	29/220	0.86 (0.48-1.54)	49/368	0.88 (0.56-1.37)	
Distal colon and rectal adenomas					
Arg/His + Arg/Arg	36/178	1 (Reference)	53/284	1 (Reference)	P = 0.99
His/His	62/220	1.42 (0.88-2.28)	86/368	1.34 (0.91-1.97)	

†Numbers of cases/controls; ‡Adjusted for age, hospital, Self-Defense Forces rank, body mass index, cigarette smoking.

1.08-3.00), particularly with distal colon and rectal adenomas (OR, 2.43; 95% CI, 1.17-5.03).

Adjusted odds ratio (OR) and 95% confidence interval (95% CI) of *ADH1B Arg47His* for colorectal adenomas by *ALDH2 Glu487Lys* and *MTHFR C677T* were examined along with site of adenomas (Table 3 and Table 4, respectively). There were no clear interactions between *ADH1B* and *ALDH2* polymorphisms, and between *ADH1B* and *MTHFR* polymorphisms on the risk of colorectal adenoma at any site.

Discussion

The *ADH1B Arg47His* polymorphism showed no measurable association with the risk of colorectal adenoma on either overall analysis or stratified analysis with alcohol consumption. Potential gene-gene interactions between *ADH1B Arg47His* and *ALDH2 Glu487Lys*, and between *ADH1B Arg47His* and *MTHFR C677T* were investigated according to site of colorectal adenomas, however, there were no appreciable interactions.

To our knowledge, no studies on the role of the *ADH1B* polymorphism in colorectal adenomas have been reported, and only three studies (Giovannucci et al., 2003; Tiemersma et al., 2003; Jung et al., 2008) have examined the association between the *ADH1C* polymorphism and risk of colorectal adenomas taking into account alcohol consumption. A case-control study in the Netherlands reported that high alcohol consumption (≥10 drinks/week) was associated with an increased risk of colorectal adenomas; the risk was significantly higher for men with the rapidly metabolizing polymorphism of *ADH1C* than for men with the slowly metabolizing polymorphism (Tiemersma et al., 2003). In contrast, the Health Professionals Follow-up Study in United States showed that heavy drinkers (>30 g/day) with the slowly metabolizing polymorphism of *ADH1C* tended to be at a greater risk for colorectal adenomas (OR, 2.94; 95% CI, 1.24-6.92) (Giovannucci et al., 2003). Another study reported that the slowly metabolizing polymorphism of *ADH1C* was associated with an approximately 2-fold increased risk for adenoma among individuals who consumed large amounts of alcohol (>26 g/day), whereas individuals with the rapidly metabolizing polymorphism of *ADH1C* were not at an increased risk of adenoma, and the interaction was statistically significant (Jung et al., 2008). Two Japanese studies reported a positive association between the *ADH1B* polymorphism and colorectal cancer, showing an increase in the risk of colorectal cancer with increasing numbers of the slow *ADH1B 47Arg* allele, but neither study showed an interaction between the *ADH1B* polymorphism and alcohol consumption for risk of colorectal cancer (Matsuo et al., 2006; Yin et al., 2007). On the other hand, the *ADH1C* polymorphism was unrelated to colorectal cancer in two studies of Caucasians (Chen et al., 2001; van der Logt et al., 2006). In the present study, the *ADH1B Arg47His* polymorphism showed no measurable association with the risk of colorectal adenoma on either overall analysis or stratified analysis with alcohol consumption. Meanwhile, the *ADH1B 47His/His* genotype was associated with a increased risk of colorectal adenomas, especially in distal colon and rectal adenomas among <30 mL/day drinkers. It was possible that individuals with the *47His/His* genotype who consumed even small amounts of alcohol might be subject to the increased risk of colorectal adenoma. However, it could be ascribed to be a chance because there were a small sample size.

The site-specific analysis is of interest because different molecular alterations have been implicated in carcinogenesis in the proximal and distal sites of the colorectum (Richman and Adlard, 2002). Genetic alterations such as K-ras and p53 mutations were shown to be more frequent in the distal site, while microsatellite instability was almost exclusively associated with proximal colon cancer (Thibodeau et al., 1993; Breivik et al., 1997; Elsaleh et al., 2000; Soong et al., 2000). This study showed that the individuals with the *ADH1B 47His/His* genotype was associated with an increased risk of distal and rectum adenoma.

Our previous studies indicated that the *ALDH2 487Lys* allele was not associated with an increased risk of colorectal adenoma and that there was an interaction between the *ALDH2 Glu487Lys* polymorphism and alcohol consumption (Hirose et al., 2005). Acetaldehyde accumulates in individuals who are fast alcohol metabolizers and slow acetaldehyde metabolizers (Tanaka et al., 1996). Thus, we hypothesized that the combination of *ADH1B His/His* and the *ALDH2 487Lys* allele might result in an increased risk of colorectal adenomas, but the current data could not confirm the effect. Alcohol and acetaldehyde exert adverse effects on folate metabolism (Mason and Choi, 2005); high alcohol consumption results in insufficient folate levels by decreasing intestinal absorption of folate and increasing renal excretion. It is hypothesized that low folate levels increase the risk of colorectal cancer or adenomas by altering DNA methylation and DNA synthesis (Giovannucci, 2004; Kono and Chen, 2005). It is likely that the effect of alcohol on the development of colorectal adenomas may be the combined result of elevation in the blood concentration of acetaldehyde, and a decrease in circulating folate concentrations. But, we did not have any data on folate intake and blood concentration of folate.

Several advantages in the methodological approaches used in this study deserve discussion. The present study was the first to examine the association between the *ADH1B Arg47His* polymorphism and colorectal adenoma risk. The colonoscopies were done almost unselectively in a defined population, and the absence of polyp lesions was confirmed in the control subjects by total colonoscopy. Since the pre-retirement health examination program covered almost all men retiring from the SDF, the subjects were relatively homogeneous in terms of social background as well as age range, selection bias was negligible. The study subjects were not representative of Japanese men in the general population, but selection bias was unlikely to exist with regard to the genetic polymorphisms under study. The frequency of *ADH1B 47Arg* allele (25% in the controls) is quite similar to that observed in a random sample of adults from the general population in Japan (Matsuo et al., 2006; Yin et al., 2007).

In conclusion, the present study suggested that the *ADH1B Arg47His* polymorphism does not contribute to the risk of colorectal adenoma for any subgroup defined by alcohol drinking, as well as the genotype of *ALDH2 Glu487Lys* and *MTHFR C677T* genotypes.

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