Alcohol drinking as well as cigarette smoking has been associated with development of colorectal polyps. Asians such as Japanese, Chinese and Korean have high frequency of genetic polymorphism in low Km aldehyde dehydrogenase (ALDH2) gene which greatly regulates alcohol intake. In the present study, we investigated associations of this polymorphism and lifestyles with colorectal polyps in self-defense forces personnel in Japan. All subjects received colonoscopy at a retirement health examination. The ALDH2 genotype was determined using polymerase chain reaction and restriction fragment length polymorphism method. Frequency of the ALDH2 genotype was not different between those with colorectal polyps (n=69) and those without the polyps (n=131). Smoking was associated with development of colorectal polyps (OR=4.7, 95% confidence interval=1.9-11.5) in the ALDH2 proficient genotype. The association appeared to be enhanced by drinking alcohol since a synergistic effect of smoking and alcohol drinking (≥60 ml/day) was indicated (OR=9.9, 95% confidence interval=2.9-34.1) by logistic regression analysis. In the ALDH2 deficient genotype, however, we could not evaluate interactions of smoking and alcohol drinking on colorectal polyp development because of the small sample size of heavy alcohol drinkers. The genotype analysis would be useful in evaluating effects of environmental factors on outcomes for each genetically defined subpopulation.

INTRODUCTION

Colorectal cancer is one of the major cause of death in developed countries. In Japan, the mortality rate from colorectal cancer has been continuously increasing for the recent 30 years. Accumulating evidence from molecular, clinical, and epidemiological studies suggests that colorectal adenomas are the major form of precursors of colorectal cancer. Furthermore, removal of colorectal polyps has been found to be effective in preventing the occurrence of colorectal cancer. Risk factors for colorectal tumors are of increasing concern. Although most epidemiological studies have reported a significant association between smoking and colorectal adenomas, only several lines of evidence exist for link between cigarette smoking and colorectal cancer. Other risk factors have also been linked with colorectal adenomas, including physical activity, waist-hip ratio, fatherhood, dietary patterns and serum ferritin levels.

Furthermore, alcohol drinking has been associated with both colorectal adenomas and colorectal cancer. Among Orientals, there exists a highly frequent genetic polymorphism in low Km aldehyde dehydrogenase (ALDH2) gene which considerably affects both alcohol sensitivity and alcohol drinking behavior. Recently, alcoholics with the...
atypical ALDH2 genotype with low ALDH2 activity have been shown to be more susceptible to development of esophageal cancer than the typical genotype 32,33, suggesting a role of acetaldehyde in the carcinogenic step. Since acetaldehyde is likely to be produced in colorectal lumen 34-36 and has been shown to be carcinogenic 37, it is of importance to determine the role of acetaldehyde in colorectal tumorigenesis.

In the present study, we assessed an effect of the ALDH2 genotype as well as alcohol drinking and cigarette smoking on development of colorectal adenomatous polyps discovered newly at a retirement health examination for self-defense forces (SDF) personnel.

MATERIALS AND METHODS

Subjects were 69 men aged 52.1 ± 1.1 (mean ± SD) years with histologically confirmed colorectal adenomas and 131 men aged 52.1 ± 1.0 years with normal colonoscopy up to ileocecal junction. They were identified among 380 male Self-Defense Forces personnel who received a retirement health examination at the Self-Defense Forces Tokyo Central Hospital between April 1993 and December 1993 and were enrolled in the present study with informed consent. Details of the examination were as described previously 38.

During the health examination, the colonoscopy was routinely performed to examine the colon and rectum. The distance of intubation and the nature of polyps were recorded. Through the examination period, 14 men with colorectal polyps were excluded because of a prior history of colorectal polyps, polypectomy, or colectomy (9), or of malignant neoplasms (1), or because of the concurrent presence of colorectal cancer (2) or other malignant neoplasms (2) and 166 men with normal colonoscopy were excluded because of a prior history of colorectal polyps, polypectomy, colectomy, or malignant neoplasms (12), because of the concurrent presence of colorectal cancers (1), contracting polyposis (74), or other bowel diseases (34), because of colonoscopy not reaching ileocecum (43) or because colonoscopy was not performed (2). Among the 69 cases, 43 men had polyps in sigmoid colon, 8 men had polyps in both colon and rectum, and 2 men had only a rectal polyp.

A self-administered questionnaire was used to determine individuals’ smoking habits, alcohol consumption or other lifestyles before receiving the colonoscopy. Cigarette-years were calculated as the average number of cigarettes consumed per day multiplied by the total years of smoking. Average amounts of alcohol consumption per day were estimated from drinking frequency and amounts of alcohol consumption per occasion. The SDF rank was classified into low, middle and high ranks.

The ALDH2 genotype was determined using PCR-RFLP method as described previously 39. Briefly, DNA was extracted from 0.1 ml of whole blood using an Isoquick kit (MicroProbe, Garden Grove, CA). Exon 12 of the ALDH2 gene was amplified by 40 cycles of PCR (1 min at 94°C, 10 sec at 52°C, and 30 sec at 72°C). PCR products were digested with Ksp632I (Boehringer Mannheim, Mannheim, Germany) and separated on agarose gels.

We used a chi-square test corrected for continuity in a comparison of the ALDH2 genotype frequency between cases and controls and in comparisons of the frequencies of current smokers and drinkers between the ALDH2 genotypes. Unconditional logistic regression analysis was utilized in an estimation of odds ratio (OR) to control for possible confounding effects of body mass index, exercise, and rank. In the estimation of OR for smoking or alcohol drinking, the effect of amounts of alcohol consumption or cigarette-years, respectively, was also controlled. The OR and 95% confidence interval (CI) were calculated using the regression coefficient and its standard error for an indicator term corresponding to a level of an independent variable. All statistical analyses were performed using the SAS version 6.08 program with the MSP Fujitsu computer system in the Data Processing Center of Kyoto University.

RESULTS

As shown in Table 1, similar frequencies of the ALDH2 genotype were observed between the cases with colorectal polyps and the controls. Allele frequencies of the ALDH2*1 and ALDH2*2 were 0.783 and 0.217 in the cases, and 0.790 and 0.210 in the controls, respectively. No significant difference ($\chi^2=0.002$) in the allele frequencies were observed between the cases and the controls. Deviation from Hardy-Weinberg’s prediction was not significant in both the cases ($\chi^2=0.796$) and the controls ($\chi^2=0.872$).

When we combined the cases and controls, the frequencies of current drinker were 92.6%, 75.3%, and 0.0% in ALDH2*1/*1, ALDH2*1/*2, and ALDH2*2/*2, respectively. All the differences in the frequencies between the ALDH2 genotypes were significant (P<0.005). Likewise, the frequencies of current smokers were 34.7%, 53.4%, and 50.0% in the three ALDH2 genotypes, respectively. The difference between ALDH2*1/*1 and ALDH2*1/*2 was significant (P<0.05).

Effects of smoking and alcohol drinking were evaluated by logistic regression analyses adjusting for body mass index, time spent for sports, rank, and for either smoking or alcohol drinking. Because of a small sample size of ALDH2*2/*2, we excluded this genotype from the analysis in the ALDH2*1/*1

| Group          | ALDH2*1/*1 | ALDH2*1/*2 | ALDH2*2/*2 | Total |
|----------------|------------|------------|------------|-------|
| Cases          | 41 (59.4%) | 26 (37.7%) | 2 (2.9%)   | 69    |
| Controls       | 80 (61.1%) | 47 (35.9%) | 4 (3.1%)   | 131   |

a) The number in each parenthesis indicates the percentage
and the total (ALDH2*1/*1 and ALDH2*1/*2) group, those with moderate smoking (≥400 cigarette-years) had a significantly high OR. In the ALDH2*1/*2 group, the moderate smoking group showed a higher but not significant OR.

As for alcohol drinking, a higher but not significant OR was observed in the ALDH2*1/*1 group. In the ALDH2*1/*2 group, a sample size was too small for the evaluation.

We also assessed the interactive effects of smoking (≥400 cigarette-years) and alcohol use (≥60 ml/day) in logistic regression analysis adjusting for body mass index, time spent for sports, and rank. As shown in Table 3, a synergistic effect of smoking and alcohol use was suggested in the ALDH2*1/*1 and the total group. In the ALDH2*1/*2 group, a small sample size of the heavy alcohol users precluded analysis of the interactive effects.

**DISCUSSION**

The present study has advantages over other studies in that study subjects were derived from a homogeneous population with regard to age, ethnicity, and occupation.

Alcohol drinking has been associated with both colorectal adenomas \cite{7,8,11-14,20} and colorectal cancer \cite{25,26,38,39}, although other studies have found lack of associations between alcohol use and colorectal cancers \cite{40}.

We could find no association between alcohol use and adenomatous polyps, regardless of the ALDH2 genotype. Logistic regression analysis, however, did reveal a significant synergistic effect between smoking and heavy amounts of alcohol use (≥60 ml/day) in the ALDH2*1/*1 genotype. Thus, alcohol use may work as an enhancer for smoking-induced tumorigenesis in this genotype. On the other hand, in the ALDH2*1/*2 genotype, a small sample size of the heavy alcohol drinkers precluded analysis of the synergism. The observed synergism between smoking and alcohol use is consistent with a previous study \cite{40}.

Yokoyama et al. \cite{32,33} have reported that alcoholics with the atypical ALDH2 genotype with less ALDH2 activity are more susceptible to development of esophageal cancer or multiple primary upper aerodigestive tract cancer than the ALDH2*1/*1 genotype, suggesting a role of acetaldehyde in the carcinogenic step. Acetaldehyde is very active and induces a numerous bio-

| Table 2. Effects of smoking and alcohol drinking on the occurrence of colon polyps in the two ALDH2 genotypes. |
|---------------------------------------------------------------|
| **Group** | **ALDH2*1/*1** | **ALDH2*1/*2** | **Total** |
| Smoking (Cigarette-years) |  |  |
| 0-399 | Controls No. | Cases No. | OR*1 (95% CI) | Controls No. | Cases No. | OR*1 (95% CI) | Controls No. | Cases No. | OR*1 (95% CI) |
|  | 56 | 14 | 1.0 (referent) | 22 | 9 | 1.0 (referent) | 78 | 23 | 1.0 (referent) |
| ≥400 | 24 | 27 | 4.7 (1.9-11.5) | 25 | 17 | 1.7 (0.6-4.6) | 49 | 44 | 3.0 (1.6-5.7) |
| Alcohol drinking (ml/day) |  |  |
| <60 | Controls No. | Cases No. | OR*1 (95% CI) | 43 | 25 | 1.0 (referent) | 112 | 53 | 1.0 (referent) |
| ≥60 | 11 | 13 | 2.4 (0.8-7.3) | 4 | 1 | 0.2 (0.02-2.6) | 15 | 14 | 1.4 (0.6-3.5) |
| a) Adjusted for body mass index, time spent for sports, and rank |
| b) Including both the ALDH2*1/*1 and ALDH2*1/*2 genotypes |

| Table 3. Interaction of smoking and alcohol drinking on the occurrence of colon polyps in the two ALDH2 genotypes. |
|---------------------------------------------------------------|
| **Risk factors** | **ALDH2*1/*1** | **ALDH2*1/*2** | **Total** |
| Smoking(-)/Alcohol(-) | 51 | 13 | 1.0 (Reference) | 21 | 9 | 1.0 (Reference) | 72 | 22 | 1.0 (Reference) |
| Smoking(-)/Alcohol(+) | 5 | 1 | 1.2 (0.1-12.1) | 1 | 0 | .c) | 6 | 1 | 0.6 (0.1-5.8) |
| Smoking(+)Alcohol(-) | 18 | 15 | 3.2 (1.3-8.2) | 22 | 16 | 1.8 (0.7-5.0) | 40 | 31 | 2.5 (1.3-4.9) |
| Smoking(+)Alcohol(+) | 6 | 12 | 9.9 (2.9-34.1) | 3 | 1 | 0.8 (0.1-8.8) | 9 | 13 | 5.0 (1.8-13.6) |
| a) Adjusted for body mass index, time spent for sports, and rank |
| b) Including both the ALDH2*1/*1 and ALDH2*1/*2 genotypes |
| c) Smoking(-), cigarette-years are less than 400; Smoking(+), equal to or more than 400. |
| d) Alcohol(-), amounts of alcohol consumption (ml/day) are less than 60; Alcohol(+), equal to or more than 60. |
| e) Not determined |
logical effects including induction of DNA crosslinks, DNA breaks 43 and sister chromatid exchanges 42, formation of DNA adducts 49, and carcinogenesis in rodents 57. Thus, acetaldehyde is suspected as an ultimate carcinogen of ethanol 40.

Ingested alcohol may enter the colorectal lumen via the vascular space rather than from transit along the small intestine 34. Ethanol in the lumen is metabolized to acetaldehyde either by ADH activity in the colorectal mucosa 38 or that in colonic bacterial flora 40. Furthermore, the ALDH2 enzyme was expressed in colonic mucosa of the ALDH2*1/*1 genotype but not in the ALDH2*1/*2 genotype 30.

These previous findings indicate a possibility that the ALDH2*1/*2 genotype is more susceptible to harmful effects of acetaldehyde in colorectal mucosa. Recently we have reported that the atypical ALDH2 genotypes including both the ALDH2*1/*2 and ALDH2*2/*2 genotypes are associated with higher risk for colon cancer but not with rectal cancer 45. Thus, further studies are required to evaluate interactive effects of smoking and alcohol drinking in the ALDH2 deficient genotype.

A reduction in DNA methylation has been proposed as a causal mechanism for colorectal tumorigenesis 39, 46, 47. Ethanol administration to pregnant mice leads to hypomethylation in fetal DNA 40. Ethanol-fed rats showed increased methionine catabolism and decreased levels of hepatic S-adenosylmethionine, which may lead to hypomethylation 49. Alcohol use is associated with risk of colon cancer, when combined with inadequate intakes of methionine and folate 39. Likewise, in large adenomas, a stronger protective effect of folate is seen with high alcohol intake and a stronger risk with alcohol in subjects with low folate intake 50. Thus, DNA hypomethylation may play a role in alcohol-related carcinogenesis in colorectal tissues.

In the present study, we found a link between cigarette smoking and colorectal polyps in Japanese male self-defense force officials in the ALDH2*1/*1 and total group. This link is consistent with our previous results obtained in the self-defense force officials in other areas of Japan 8, 11, 12, and also with results in other countries 7, 9, 10, 13-19. The association of smoking with colorectal polyps may be further strengthened by drinking heavy amounts of alcohol in the ALDH2*1/*1, because a synergistic effect of smoking and heavy alcohol drinking was indicated in this genotype as mentioned above. Probably those with this genotype drink more because they are less sensitive to alcohol 26, 31, 51.

Lack of association between cigarette smoking and colorectal cancer has been reported in many previous papers 16, 40, 52, 53, whereas several prospective and retrospective studies describe positive association between them 9, 10, 16, 17, 54, 55. Giovannucci et al. 9, 10, 18 have suggested that cigarette smoking more than 35 years in the past is associated with the risk for colorectal cancer. Slattery et al. 56 have recently reported a positive association between them in a case-control study with participants from the Kaiser Permanente Medical Care Program. In cancer case-control studies, inclusion of subjects with adenomas in the control group may mask the association between cigarette smoking and risk of colorectal cancer 57. More epidemiological studies taking into account a long incubation period between smoking and occurrence of cancers 40 are needed to determine a role of cigarette smoking in colorectal carcinogenesis.

The observed difference in smoking rates between the two ALDH2 genotype is unexpected because we did not see any difference in the proportion of smokers between the three ALDH2 genotypes in Japanese male workers (n=424; data not shown). Thus, the difference may be due to chance. Alternatively, it may be possible that those with the ALDH2 deficient type (ALDH2*1/*2) is likely to smoke more to reduce their stresses because they cannot drink alcohol so much.

In summary, we investigated for the first time the association between alcohol use, the genetic factor regulating drinking behavior and colorectal polyps. We found that smoking was associated with development of colorectal polyps in the ALDH2 proficient genotype. The association was enhanced by drinking heavy amounts of alcohol. In the ALDH2 deficient genotype, however, we could not evaluate interactions of smoking and alcohol drinking on colorectal polyp development because of the small sample size of heavy alcohol drinkers. The genotype analysis would be useful in evaluating effects of environmental factors on outcomes for each genetically defined subpopulation.

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