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Cigarette Smoking, *CYP1A1 Msp*I and *GSTM1* Genotypes, and Colorectal Adenomas[1]

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ABSTRACT

Cigarette smoking has been related to increased risk of colorectal adenomas, but the underlying mechanisms are unknown. Genetic polymorphisms are known for enzymes involved in the activation of polycyclic aromatic hydrocarbons and other tobacco-related carcinogens. Polycyclic aromatic hydrocarbons are activated by cytochrome P4501A1 (CYP1A1) and detoxified by glutathione *S*-transferases. We investigated the relation of *CYP1A1 Msp*I and *GSTM1* genotypes to the risk of colorectal adenomas with special reference to interaction with cigarette smoking among 205 cases of colorectal adenomas and 220 controls with normal total colonoscopy in a male Japanese population. Cigarette smoking was strongly associated with increased risk of colorectal adenomas. Overall, neither the *CYP1A1 Msp*I genotype nor the *GSTM1* genotype was related to colorectal adenomas. A significant trend for increased risk of colorectal adenomas associated with smoking was observed for each of the *CYP1A1 Msp*I genotypes, and the increasing trends did not differ by *Msp*I genotype. The positive association between smoking and colorectal adenomas did not vary much with *GSTM1* genotypes. Among former and current smokers, adenoma risk did not differ according to the combination of *CYP1A1 Msp*I and *GSTM1* genotypes. *CYP1A1 Msp*I and *GSTM1* genotypes do not seem to modify the risk of colorectal adenomas associated with cigarette smoking.

INTRODUCTION

Many studies have consistently found cigarette smoking to be associated with an increased risk of colorectal adenomas (1, 2), a well-established precursor lesion of colorectal cancer (3). Whereas earlier studies have generally failed to find a positive association between smoking and colorectal cancer (4), two prospective studies in the United States demonstrated an increased risk of colorectal cancer associated with smoking in the distant past (several decades prior to the study), suggesting that smoking may be linked with the initiation of colorectal carcinogenesis (5, 6). However, little is known about the biological mechanisms with regard to the role of tobacco smoke in colorectal carcinogenesis.

Genetic polymorphisms are known for enzymes involved in the activation of tobacco-related carcinogens such as PAHs,[3] nitrosamines, and arylamines. PAHs are activated by CYP1A1, a phase I drug-metabolizing enzyme, into reactive forms that produce DNA adducts, and the reactive metabolites of PAHs are detoxified by glutathione *S*-transferases, a phase II enzyme. A rare mutation at the *Msp*I site in the *CYP1A1* gene has been reported to be associated with an increased risk of lung cancer, particularly of squamous cell carcinoma (7, 8). There is an ethnic difference in the frequency of the *CYP1A1 Msp*I mutation allele, and the homozygous *Msp*I mutation is relatively common in the Japanese population (9). Interestingly, a case-control study of Japanese men in Hawaii reported an 8-fold increase in the risk of colorectal *in situ* carcinoma associated with *Msp*I homozygous mutation (10). The relation between *GSTM1* polymorphism and cancer risk has also drawn much interest recently (11). At least six studies have addressed the relation between the *GSTM1*-null genotype and colorectal cancer or adenomas. Whereas two of these studies suggested an increased risk among those with the *GSTM1*-null genotype (12, 13), others found no difference in the risk between the *GSTM1*-null genotype and the non-null genotype (14–17). None of these studies examined the combined effect of *CYP1A1 Msp*I and *GSTM1* genotypes. We investigated the relation of the *CYP1A1 Msp*I variant genotype and the *GSTM1*-null genotype to the risk of colorectal adenomas with special reference to interaction with cigarette smoking in middle-aged Japanese men.

MATERIALS AND METHODS

Subjects. Study subjects were men who received a preretirement health examination at the SDF Fukuoka Hospital between January 1995 and December 1996 and at the SDF Kumamoto Hospital between May and December 1996. Retiring self-defense officials receive a comprehensive medical examination that includes colonoscopy and blood biochemical measurements as routine procedures during a 5-day admission. Details of the health examination have been described elsewhere (2, 18). With written informed consent, 7 ml of blood were taken for genetic analysis.

Of 803 men in the consecutive series, 778 underwent total or partial colonoscopy. Excluded from the study were 41 men with a prior history of colorectomy ($n = 3$), colorectal polypectomy ($n = 36$), or malignant neoplasms ($n = 4$). The macroscopic findings of the colonoscopy among 737 men were as follows: (*a*) normal, 368 men; (*b*) polyps, 325 men; (*c*) carcinoma, 2 men; and (*d*) other lesions, 42 men. A total of 209 of 325 men with colorectal polyps were found to have histologically confirmed colorectal adenomas without *in situ* or invasive carcinoma; the histological findings of the remaining 116 men were no biopsy ($n = 16$), normal or inflammatory tissue ($n = 63$), hyperplastic polyp without adenoma ($n = 34$), carcinoid ($n = 1$), and carcinoma ($n = 2$). Of the 368 men with normal study results, 230 men who had received total colonoscopy were used as controls; the colorectum of the remaining 138 men was not completely examined. Blood samples for DNA analysis were not available for 4 cases of adenomas and 10 controls, and the present study finally used 205 cases of colorectal adenomas and 220 controls with normal total colonoscopy.

Adenomas located more than 60 cm from the anus were defined as proximal adenomas, and the others were defined as distal adenomas. Cases with proximal adenomas only, distal adenomas only, and both proximal and distal adenomas numbered 69, 110, and 26, respectively. Those with both proximal and distal adenomas were treated as proximal adenoma cases. Cases with an adenoma of <5 mm, 5+ mm, and unknown size (diameter of the largest adenoma in multiple adenoma cases) numbered 129, 71, and 5, respectively.

Smoking and Alcohol Use. Information on smoking habits, alcohol use, and other lifestyle factors was obtained before colonoscopy by use of a self-administered questionnaire, with a supplementary interview for unanswered questions. Subjects were asked whether they were lifelong nonsmokers, former smokers, or current smokers, and former and current smokers reported the average number of cigarettes smoked per day and the number of

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[3] The abbreviations used are: PAH, polycyclic aromatic hydrocarbon; SDF, Self Defense Forces; OR, odds ratio; CI, confidence interval.

years of smoking. Cumulative exposure to cigarette smoking was expressed by cigarette-years, the number of cigarettes smoked per day multiplied by years of smoking. Alcohol drinkers were defined as those having ever drunk alcohol at least once a week over a period of 1 year or longer. Former alcohol drinkers were separated from lifelong nondrinkers. For current alcohol drinkers, alcohol consumption was estimated from reported frequencies and amounts of consumption of five types of alcoholic beverages (sake, shochu, beer, spirits, and wine) on average in the past year.

Laboratory Analysis. Genomic DNA was extracted from buffy coat stored at −80°C using the QIAamp blood kit (QIAGEN, Santa Clarita, CA). The genotype of the *CYP1A1 Msp*I polymorphism was determined by the PCR-RFLP method as described by Hayashi *et al.* (19). The PCR products of a 340-base region containing the *Msp*I restriction site were digested with *Msp*I (Nippon Gene, Toyama, Japan) and subjected to electrophoresis to identify wild-type homozygotes (genotype A), heterozygotes (genotype B), and variant homozygotes (genotype C). The *GSTM1*-null genotype was determined by PCR analysis using the method described by Zhong *et al.* (12). All PCR assays were done by one of the authors (H. I.) without knowledge of adenoma status.

Statistical Analysis. Logistic regression analysis was used to examine the relation of cigarette smoking and genetic polymorphism to colorectal adenomas. Statistical adjustment was made for cigarette smoking, alcohol use, body mass index, hospital, and rank in the SDF. Age was not taken into account because age was in a limited range (47–55 years). Cigarette smoking was categorized into 0, 1–399, 400–799, and 800+ cigarette-years; subjects were also classified into lifelong nonsmokers, past smokers, and current smokers consuming <25 or 25+ cigarettes/day. Alcohol use was categorized into never, past, and current use with a consumption of <30, 30–59, or 60+ ml of alcohol per day; and rank in the SDF was categorized into low, middle, and high ranks. Body mass index was used as a continuous variable. Indicator variables were created for the categories of the covariates. ORs and 95% CIs were calculated from logistic regression coefficients and SEs for the corresponding indicator variables. The trend for association between cigarette-years and adenoma risk was tested by the Wald statistic in logistic regression analysis with ordinal scores of 0, 1, 2, and 3 assigned to the four levels of cigarette smoking. Interaction between the genotypes and cigarette smoking on the risk of colorectal adenomas was assessed by the likelihood ratio test using an ordinal variable for cigarette-years (which were scored from 0–3). Two-sided *P* values less than 0.05 were regarded as statistically significant. All statistical computations were done by using PC-SAS version 6.12 software (SAS Institute, Inc., Cary, NC).

RESULTS

There was a strong, positive association between cigarette smoking and colorectal adenomas, regardless of the adjustment for alcohol use, body mass index, rank in the SDF, and hospital (Table 1). Whereas the OR for past smokers compared with lifelong nonsmokers did not differ much from unity, current smokers showed a nearly 4-fold increase in the ORs. When the association with smoking was examined in terms of cigarette-years, the ORs increased progressively with increasing levels of cumulative exposure.

Table 1 *Relation between cigarette smoking and colorectal adenomas*

Variable	No. of men (%)		Crude OR (95% CI)	Adjusted OR[a] (95% CI)
	Case	Control		
Smoking				
Never smoker	35 (17.1)	73 (33.2)	1.0	1.0
Past smoker	41 (20.0)	72 (32.7)	1.2 (0.7–2.1)	1.1 (0.6–1.9)
<25 cigarettes/day	83 (40.5)	51 (23.2)	3.4 (2.0–5.8)	3.5 (2.0–6.1)
25+ cigarettes/day	46 (22.4)	24 (10.9)	4.0 (2.1–7.6)	3.8 (2.0–7.4)
Cigarette-years				
0	36 (17.6)	73 (33.2)	1.0	1.0
1–399	34 (16.6)	47 (21.4)	1.5 (0.8–2.7)	1.4 (0.8–2.6)
400–799	91 (44.4)	80 (36.4)	2.3 (1.4–3.8)	2.2 (1.3–3.6)
800+	44 (21.5)	20 (9.1)	4.5 (2.3–8.7)	4.1 (2.1–8.2)
Trend[b]			$P = 0.0001$	$P = 0.0001$

[a] Adjusted for hospital, rank in the SDF, alcohol use, and body mass index.
[b] Ordinal scores 0, 1, 2, and 3 were assigned to the four levels of cumulative exposure.

Table 2 *CYP1A1 MspI and GSTM1 genotypes and colorectal adenomas in Japanese men*

Genotype	No. of men (%)		Crude OR (95% CI)	Adjusted OR[a] (95% CI)
	Adenoma case	Control		
*CYP1A1 Msp*I				
A	86 (42.0)	87 (39.5)	1.0	1.0
B	90 (43.9)	94 (42.7)	1.0 (0.6–1.5)	1.0 (0.7–1.6)
C	29 (14.1)	39 (17.7)	0.8 (0.4–1.3)	0.8 (0.4–1.4)
GSTM1				
Non-null	97 (37.3)	97 (44.1)	1.0	1.0
Null	108 (52.7)	123 (55.9)	0.9 (0.6–1.3)	0.9 (0.6–1.4)

[a] Adjusted for hospital, rank in the SDF, cigarette-years, alcohol use, and body mass index.

Table 3 *CYP1A1 MspI and GSTM1 genotypes and colorectal adenomas by location of adenomas in Japanese men*

Genotype	Proximal adenomas		Distal adenomas	
	No.	Adjusted OR[a] (95% CI)	No.	Adjusted OR[a] (95% CI)
*CYP1A1 Msp*I				
A	47	1.0	39	1.0
B	36	0.7 (0.4–1.2)	54	1.4 (0.8–2.4)
C	12	0.5 (0.2–1.1)	17	1.0 (0.5–2.2)
GSTM1				
Non-null	46	1.0	51	1.0
Null	49	0.9 (0.5–1.5)	59	0.9 (0.6–1.5)

[a] Adjusted for hospital, rank in the SDF, alcohol use, cigarette-years, and body mass index.

The genotype distribution was almost identical between adenoma cases and controls with regard to both *CYP1A1 Msp*I and *GSTM1* (Table 2). Thus, the risk of colorectal adenomas, in terms of the OR, did not vary with either of the two genetic polymorphisms, regardless of whether the covariates were adjusted for or not. The associations did not change when adjustment was made for current smoking status (never, past, <25 or 25+ cigarettes/day) instead of cigarette-years (data not shown).

Adenoma risk associated with genetic polymorphism was examined separately for proximal and distal adenomas (Table 3). *CYP1A1 Msp*I genotype C was associated with a statistically nonsignificant decrease in the risk of proximal adenomas but not of distal adenomas. *GSTM1* genotype was not related to either proximal or distal adenomas. No apparent difference was noted between small and large adenomas with regard to the association with either *CYP1A1 Msp*I or *GSTM1* genotype (data not shown).

Table 4 presents the ORs of colorectal adenomas according to the combination of smoking levels and *CYP1A1 Msp*I genotypes. As compared with lifelong nonsmokers with genotype A, nonsmokers with genotype C showed a statistically significant decrease in adenoma risk. The OR for the highest level of cigarette smoking was approximately 2-fold greater in those with genotype A than in those with genotypes B or C, but the 95% CIs overlapped well. Increasing trends of ORs with increasing levels of cigarette smoking were statistically significant within each group of genotypes and did not differ significantly according to the genotype (interaction $P = 0.31$).

The relation between smoking and colorectal adenomas did not vary much by *GSTM1* genotype (Table 5). Although the association with cigarette smoking tended to be slightly stronger in those with the *GSTM1* non-null genotype than in those with the null genotype, the interaction between the *GSTM1* genotype and smoking was not statistically significant ($P = 0.35$).

We further examined the effect of *CYP1A1 Msp*I and *GSTM1* genotypes in combination among former and current smokers (Table 6). Results from the analysis of current smokers only were almost the same as those for former and current smokers combined (data not

Table 4 *Relation of cigarette smoking and CYP1A1 MspI polymorphism to colorectal adenomas*

	Genotype A		Genotype B		Genotype C	
Cigarette-years	No.[a]	OR[b] (95% CI)	No.[a]	OR[b] (95% CI)	No.[a]	OR[b] (95% CI)
0	14/20	1.0	19/33	1.0 (0.4–2.5)	3/20	0.2 (0.1–0.9)
1–399	14/21	1.0 (0.4–2.7)	15/22	1.0 (0.4–2.7)	5/4	1.8 (0.4–8.4)
400–799	39/40	1.5 (0.6–3.5)	36/28	1.9 (0.8–4.5)	16/12	1.9 (0.7–5.3)
800+	19/6	5.1 (1.6–16.6)	20/11	2.5 (0.9–7.1)	5/3	2.2 (0.4–11.0)
Trend[c]		$P = 0.007$		$P = 0.03$		$P = 0.002$

[a] Number of cases/controls.
[b] Adjusted for hospital, rank in the SDF, alcohol use, and body mass index.
[c] Tested for each category of *CYP1A1 Msp*I with ordinal scores 0, 1, 2, and 3 assigned to the four levels of cigarette-years.

shown). There was no variation in the risk of colorectal adenomas according to the categories of the two genotypes. Because of the limited number of subjects, analysis of these two genetic polymorphisms in combination was not possible for nonsmokers.

DISCUSSION

The finding that cigarette smoking was related to an increased risk of colorectal adenomas is consistent with previous SDF study observations (2) as well as many studies in Western countries (1). The present study adds to the evidence that cigarette smoking is associated with an increased risk of colorectal adenomas.

Homozygous mutant allele (genotype C) at *CYP1A1 Msp*I is rare in Caucasians but is relatively common in the Japanese. Thus, the Japanese are a suitable population for study of the role of *CYP1A1 Msp*I polymorphism in human carcinogenesis. The prevalence of genotype C in the control subjects of the present study was comparable to those reported among healthy subjects in Japan (9). The present study showed no association between *CYP1A1 Msp*I genotype and colorectal adenomas as a whole. The risk of proximal but not distal adenomas tended to be lower among men with genotype C as compared with those with genotype A. Unexpectedly, genotype C was associated with a decreased risk of colorectal adenomas among nonsmokers. The findings are in disagreement with the observation regarding *in situ* colorectal cancer in a Japanese population in Hawaii (10). In that study, an approximately 8-fold increased risk was observed in association with genotype C. Genotype C accounted for only 4% of the control subjects in the Hawaiian Japanese study; this figure is much lower than that observed in the present study and elsewhere in Japan (9). The observed protective association between genotype C and colorectal adenomas among nonsmokers may be due to chance because the number of men with genotype C was still small. Although much larger studies are needed to clarify the role of the *CYP1A1 Msp*I genotype in colorectal carcinogenesis, the present study provides no evidence that *CYP1A1 Msp*I genotype C confers increased susceptibility to colorectal adenomas in conjunction with exposure to cigarette smoking. An accentuated effect of smoking among those with genotype C has also been observed for squamous cell carcinoma of the lung (8). Increased inducibility of aryl hydrocarbon hydroxylase, an enzyme activating PAHs, was recently observed among subjects with genotype C (20). Compounds other than PAHs in tobacco smoke may also be responsible for the occurrence of colorectal adenomas.

Table 5 *Relation between cigarette smoking and colorectal adenomas by GSTM1 polymorphism*

	Non-null		Null	
Cigarette-years	No.[a]	OR[b] (95% CI)	No.[a]	OR[b] (95% CI)
0	19/37	1.0	17/36	1.1 (0.5–2.5)
1–399	13/22	1.2 (0.5–2.8)	21/25	1.7 (0.7–3.8)
400–799	39/27	2.9 (1.4–6.2)	52/53	1.9 (1.0–3.8)
800+	26/11	4.6 (1.8–11.4)	18/9	4.0 (1.5–10.7)
Trend[c]		$P = 0.0001$		$P = 0.03$

[a] Number of cases/controls.
[b] Adjusted for hospital, rank in the SDF, alcohol use, and body mass index.
[c] Tested for each category of *GSTM1* with ordinal scores 0, 1, 2, and 3 assigned to the four levels of cigarette-years.

Table 6 *Adjusted ORs (95% CI) of colorectal adenomas according to CYP1A1 MspI and GSTM1 genotypes among former and current smokers*

		No.		
CYP1A1	*GSTM1*	Cases	Controls	OR[a] (95% CI)
A	Non-null	32	28	1.0
A	Null	40	39	0.9 (0.4–1.8)
B	Non-null	35	24	1.2 (0.6–2.6)
B	Null	36	37	0.8 (0.4–1.6)
C	Non-null	11	8	1.1 (0.4–3.3)
C	Null	15	11	1.1 (0.4–2.8)

[a] Adjusted for hospital, rank in the SDF, alcohol use, and body mass index.

The frequency of the *GSTM1*-null genotype has been reported to be approximately 50% in Japanese as well as in Caucasian populations (11). In the present study, half of both cases and controls were classified as having the *GSTM1*-null genotype. *GSTM1* polymorphism did not materially modify the relation between cigarette smoking and colorectal adenomas. Two case control studies in the United Kingdom (12) and Japan (13) reported an increased risk of colorectal cancer among those with the *GSTM1*-null genotype as compared with those with the non-null genotype. However, two other case-control studies and one prospective study failed to find an increased susceptibility to colorectal cancer among individuals with the *GSTM1*-null genotype (14–16). One of these studies was based on nearly 2000 cases of colorectal cancer and observed no interaction with various indices of smoking (16). A study of colorectal adenomas also found neither an overall association with the *GSTM1*-null genotype nor an interaction between the null genotype and smoking habits (17). Our findings corroborated the lack of effect of the *GSTM1*-null genotype on colorectal adenomas.

GSTs have four classes of isoenzymes, *i.e.*, α, μ, π, and theta (21). *GSTM1* genotype is only one of several genetic determinants of glutathione *S*-transferase activity. Although GSTM1 is considered to be a critical enzyme detoxifying reactive metabolites of PAHs, other isoenzymes, especially glutathione *S*-transferase T, may also function in the detoxification of tobacco-related carcinogens (21). Thus, the lack of an association between the *GSTM1*-null genotype and colorectal adenomas does not necessarily imply that different activities in the detoxification of PAH metabolites are irrelevant to colorectal adenomas. We expected that the risk of colorectal adenomas would be higher in smokers with *CYP1A1 Msp*I genotype C and the *GSTM1*-null genotype than in smokers having another combination of these two genetic polymorphisms. However, the present results were not in line with such a hypothesis.

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