

hOGG1 Ser326Cys Polymorphism and Lung Cancer Susceptibility¹

Haruhiko Sugimura,² Takashi Kohno, Kenji Wakai, Kiyoko Nagura, Keiichiro Genka, Hisaki Igarashi, Brian J. Morris, Satoshi Baba, Yoshiyuki Ohno, ChangMing Gao, ZhongYou Li, JianDong Wang, Toshiro Takezaki, Kazuo Tajima, Tibor Varga, Toshiko Sawaguchi, J. Koji Lum, Jeremy J. Martinson, Shoichiro Tsugane, Teruo Iwamasa, Kazuya Shimura, and Jun Yokota

Department of Pathology, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Japan [H. S., K. N., H. I., S. B., K. S.]; Biology Division, National Cancer Center Research Institute, Tokyo 104-0045, Japan [T. K., K. S., J. Y.]; Department of Preventive Medicine, Nagoya University School of Medicine, Nagoya 466-8550, Japan [K. W., Y. O.]; National Okinawa Hospital, Okinawa 901-2214, Japan [K. G.]; Hypertension Gene Laboratory and Institute for Biomedical Research, Department of Physiology, The University of Sydney, Sydney, New South Wales 2006, Australia [B. J. M.]; Cancer Institute of Jiangsu Province, Nanjing, Jiangsu, People's Republic of China [C. G., Z. L., J. W.]; Epidemiology Division, Aichi Cancer Center Research Institute, Nagoya 464-8681, Japan [T. T., K. T.]; Department of Forensic Medicine, Albert Szent Gyorgyi Medical University, Kossuth L. sg1.40, Hungary [T. V.]; Department of Legal Medicine, Tokyo Women's Medical College, Tokyo 162-8666, Japan [T. S.]; The Institute of Statistical Mathematics, Tokyo 106-8569, Japan [J. K. L.]; Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15261 [J. J. M.]; Epidemiology and Biostatistics Division, National Cancer Center Research Institute East, Chiba 277-8577, Japan [S. T.]; and Department of Pathology, Ryukyuu University School of Medicine, Okinawa 903-0125, Japan [T. I.]

Abstract

The human homologue of the yeast *OGG1* gene, *hOGG1*, has been cloned, and its genetic structure has been determined. Several polymorphisms in the *hOGG1* gene were detected in the Japanese populations, and among them, the Ser-Cys polymorphism at codon 326 has been shown to have a functional difference in complementation of mutant *Escherichia coli* that is defective in the repair of 8-hydroxyguanine. Activity in the repair of 8-hydroxyguanine is greater in *hOGG1*-Ser³²⁶ protein than in *hOGG1*³²⁶ protein. Because many environmental carcinogens produce 8-hydroxyguanine residue and mismatching to this modified base potentially causes oncogenic mutations, the capacity to repair these lesions can be involved in cancer susceptibility in human beings. We, therefore, examined allele distributions of the

Ser326Cys polymorphism in a case-control study of male lung cancer in Okinawa. The analyses based on 241 cases and 197 hospital controls disclosed the following findings. (a) Those with the Cys/Cys genotype were at an increased risk of squamous cell carcinoma and nonadenocarcinoma compared to those with the Ser/Cys and those with the Ser/Ser genotypes combined. The odds ratios adjusted for age and smoking history were 3.01 (95% confidence interval, 1.33–6.83) and 2.18 (95% confidence interval, 1.05–4.54), respectively. (b) The odds ratios for other histological subtypes of lung cancer or those in total were not significant. Those for Cys/Cys or Ser/Cys genotype against Ser/Ser did not reach statistical significance in any cell type. (c) The distributions of this polymorphism varied for different populations (Chinese, Japanese, Micronesians, Melanesians, Hungarians, and Australian Caucasians), with much less prevalence of Cys allele in the latter three populations. Although our sample size was limited, these results indicate that the Ser326Cys variant may be related to squamous cell lung cancer susceptibility. The Cys/Cys genotype appears to be more susceptible to squamous cell carcinoma, although the risk is less than that previously reported to be associated with the *CYP1A1* gene. Further studies are needed to assess the importance of the interpopulation variation to cancer susceptibility.

Introduction

Molecular cloning of a human counterpart of the yeast *OGG1* (*hOGG1*; Refs. 1–6) paved the way for possible application of *hOGG1* variants as genetic markers for individual susceptibility to various cancers. This is because 8-hydroxyguanine, assumed to be repaired by *hOGG1*, is highly mutagenic, causing a major oxidative DNA damage induced by reactive oxygen species (7, 8). Moreover, the content of 8-hydroxyguanine in DNA of nontumor lung tissue has been shown to be higher in lung cancer patients than in controls (9). Our previous structural studies as well as those by others revealed the presence of several polymorphisms inside *hOGG1* in the Japanese population (10–12). Among them, the polymorphism Ser326Cys is associated with complementation activity for *Escherichia coli* mutants that are defective in the repair of 8-hydroxyguanine (10). On the basis of our previous studies, the capacity to complement is ~7 times higher in the 326Ser protein than in the 326Cys protein, suggesting that 326Cys allele may give an individual more susceptibility to the formation of 8-hydroxyguanine in DNA (10, 11). Because previous studies suggest a role of oxidative DNA damage in lung carcinogenesis (3), we evaluated this presumably functional polymorphism of *hOGG1* in a case-control framework of human lung cancer.

Subjects and Methods

Case-Control DNA Set. Samples of DNA from lung cancer patients and hospital controls used here were the same as those

Received 2/15/99; revised 6/2/99; accepted 6/7/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ This work was supported in part by a Grant-in-Aid from the Ministry of Health and Welfare (Grant 9-2); the Ministry of Health and Welfare for the Second-Term Comprehensive 10-Year Strategy for Cancer Control; the Ministry of Education, Science, Sports and Culture; the Smoking Research Foundation; and the Uehara Memorial Foundation.

² To whom requests for reprints should be addressed, at Department of Pathology, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu 431-3192, Japan. Phone 81-53-435-2220; Fax: 81-53-435-2225; E-mail: hsugimur@hamamed.ac.jp.

used in our previous case-control study for *CYP1A1* (13). Briefly, all lung cancer patients and hospital controls were males, recruited from the National Okinawa Hospital, whose diagnoses of lung cancer were verified histopathologically and cytologically. Histological categorization was performed based on the WHO criteria (14, 15). DNA was available from 241 cases and 197 hospital controls. The cases constituted a sequential series of newly diagnosed lung cancer patients at the National Okinawa Hospital from 1993 to 1996. In our previous study (16), we showed that lung cancer patients in this hospital could represent lung cancer in Okinawa. Controls were randomly selected from in-patients at the hospital during the same study period. The participation rate was nearly 100% in both cases and controls, and only six cases were excluded from the final analysis because their diagnoses were not pathologically confirmed. The diagnoses of the controls included 19 tuberculosis, 8 cancers outside the lung, 8 benign tumors, 15 bronchopneumonia, 8 pyothorax, 7 chronic obstructive lung diseases, 29 other respiratory diseases, 13 benign liver diseases, 15 other gastrointestinal diseases, 13 diabetes, 9 fractures, 15 other orthopedic diseases, 25 neuromuscular diseases, 11 others, and 2 healthy individuals. Smoking history was obtained via interviews by doctors and nurses and was reviewed by the researchers. Smoking variables such as starting and quitting ages of smoking and numbers of cigarettes per day were also collected.

PCR-SSCP³ Analysis. The genomic structure of *hOGG1* is shown in Fig. 1. The primers used for identification of the Ser326Cys polymorphism in exon 7 were 5'-TGAATTCGGAAGGTGCTTGGGGAAT-3' and 5'-ACTGTCAGTCTCACCAG-3'. A forward primer, 5'-GGAAGGTGCTTGGGGAAT-3', without an *EcoRI* restriction site was also used for the same DNA in combination with the same backward primer, 5'-ACTGTCAGTCTCACCAG-3'. The PCR product was denatured with formamide at 95°C for 15 min, quenched on ice, and loaded to polyacrylamide gels under several conditions. Visualization was performed with a silver stain kit (Wako, Osaka, Japan) as described previously (17). Unambiguous migration differences between the two allelic bands were obtained by electrophoresis performed at room temperature and 4°C with a glycerol concentration of 12%. In addition, each allelic PCR product was cloned and sequenced to confirm the genotypes inferred from SSCP analysis. Sequencing involved a dye-primer cycle sequence kit (Amersham, Cleveland, OH) and an ABI 301 automated sequencer (Applied Biosystems, Foster City, CA).

Statistical Analysis. The strengths of associations between lung cancer and the *hOGG1* polymorphism were measured as ORs. The ORs were obtained using unconditional logistic regression analysis (18). Crude ORs and those adjusted for age and smoking habits were calculated. Because the Ser/Ser genotype was thought to have the highest effective enzymatic activity, we used this genotype as our reference for lung cancer risk. Thus, the ORs for the Ser/Cys and Cys/Cys genotypes relative to the Ser/Ser genotype were computed. The ORs for the Cys/Cys genotype versus other genotypes combined were also computed because only the Cys/Cys genotype might influence the individual repair activity. We calculated crude and age-adjusted ORs by smoking dosage, that is, cigarette-years [(cigarettes per day) × (smoking years)] of ≥800 or <800. The χ^2 test was used to test for deviations of genotype distributions

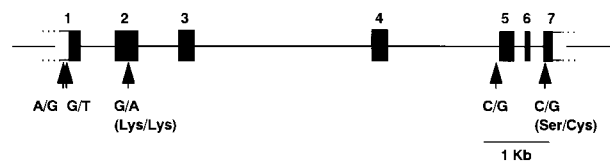


Fig. 1. Genomic structure of *hOGG1* showing previously identified polymorphic sites (10, 33, 38). The Ser-Cys polymorphism is in exon 7 (C/G) and in linkage disequilibrium with the polymorphism in intron 4 (C/G; Ref. 10).

from Hardy-Weinberg equilibrium (19). We evaluated how likely our study was to detect a significant ORs for lung cancer at 5% level, when the real ORs ranged from 1.5 to 4.0 (20), and we also calculated the required number of cases of total lung cancer, squamous cell carcinoma, adenocarcinoma, and non-adenocarcinoma (lung carcinoma other than adenocarcinoma, that is, squamous cell, small cell, large cell, and other carcinoma), based on fixed 80% power, 5% type I error, and the ORs from this study.

Population Study. Six populations that were free from cancer were studied to detect a difference in the distributions of the polymorphism among populations: Chinese in Jiangsu Province, Australian Caucasians, Hungarians (21), Japanese in Tokyo, Micronesians from the Republic of Palau and Yap State, and Melanesians from three islands of Vanuatu (22, 23). All were randomly sampled, unrelated individuals. Differences in the distributions among the populations were tested by the χ^2 test. Deviation from the Hardy-Weinberg equilibrium was also tested (19).

Results

Identification of the Ser326Cys Polymorphism by Non-Radioisotope SSCP. Electrophoresis at room temperature with 12% glycerol discriminated three genotypes, as shown in Fig. 2a. Migration patterns were different when the primers without restriction enzyme site tags were used, but the genotypes assigned were consistent (Fig. 2a). Confirmatory sequence results are shown in Fig. 2b.

Association of the Ser326Cys Polymorphism with Lung Cancer. The age distribution and smoking habits among the cases and controls for which DNA was available are shown in Table 1. The mean ages \pm SDs in cases and controls were 67.6 ± 9.2 and 62.0 ± 11.3 years, respectively. As expected, cases tended to be heavier smokers than controls. Histological subtypes of the cases were: squamous cell carcinoma, 49.0% ($n = 118$); adenocarcinoma, 32.4% ($n = 78$); small cell carcinoma, 11.6% ($n = 28$); and others, 7.0% ($n = 17$). The distribution of histological subtypes of lung cancer in Okinawa is known to be different from that in other parts of Japan (24, 25), and the distribution here described is consistent with that of lung cancer in Okinawa (25).

The distribution of the Ser326Cys polymorphism and the ORs for Ser/Cys or Cys/Cys genotype versus Ser/Ser are summarized in Table 2. The distribution among the controls was consistent with Hardy-Weinberg equilibrium; it did not deviate from the expected distribution ($P = 0.22$). For all lung cancer cases, the OR adjusted for age and smoking habits was not significantly greater than unity. The contribution of the Ser326Cys polymorphism in each histological subcategory is also shown in Table 2. The OR was not statistically significant for any lung cancer subtype. Table 3 shows the ORs for Cys/Cys genotype versus the combined Ser/Ser and Ser/Cys geno-

³ The abbreviations used are: SSCP, single-strand conformation polymorphism; OR, odds ratio; CI, confidence interval.

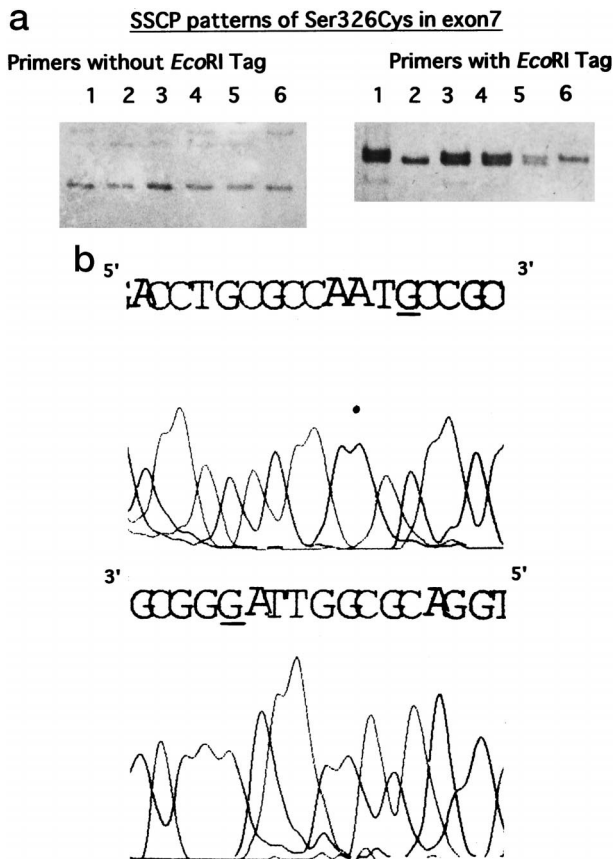


Fig. 2. *a*, three genotypes revealed by SSCP analysis in 12% polyacrylamide gels. Lanes 1, 3, 4, and 5, *Ser/Cys*; Lane 2, *Cys/Cys*; and Lane 6, *Ser/Ser*. Right, PCR products with *EcoRI* tag primers. *b*, confirmatory base substitution identification by sequencing. Differences (underlined) in a base G (*top*, *Cys* allele) and C (*bottom*, showing complimentary sequence, *Ser* allele) at codon 326 are indicated.

types. The ORs were not significant for all cases, but interestingly, in squamous cell carcinoma, homozygous *Cys/Cys* individuals showed a significantly higher risk than the other genotypes after adjustment for age and smoking history (OR = 3.01, 95% CI, 1.33–6.83; $P = 0.008$). Similarly, for nonadenocarcinoma, a significantly higher risk was also observed (OR = 2.18; 95% CI, 1.05–4.54; $P = 0.037$).

We did analyses including the other smoking variables, such as numbers of cigarettes smoked per day, the results were not materially changed (data not shown).

ORs by Smoking Dosage. The ORs by smoking dosage are shown in Tables 2 and 3. The OR for *Cys/Cys* genotype *versus* either the *Ser/Ser* homozygote or the two other genotypes combined was greater in heavy smokers (cigarette-years ≥ 800) but was not statistically significant. Further adjustment for smoking-years in each strata did not modify the ORs substantially (data not shown).

Statistical Power. Our power calculations indicated that the analyses had the power to detect an OR of 2.5 at 5% significance level in $\sim 80\%$ or more likelihood for all lung cancer cases, squamous cell carcinoma, and nonadenocarcinoma (data not shown). For other cell types and analysis by smoking dosage, however, the statistical power was found to be lower (data not shown). The required numbers of cases, based on 80%

Table 1 Age distribution and smoking habits among cases and controls

	Cases		Controls	
	No.	%	No.	%
Age (yr)				
30–39	1	0.4	7	3.6
40–49	10	4.1	19	9.6
50–59	31	12.9	52	26.4
60–69	89	36.9	70	35.5
70–79	90	37.3	40	20.3
≥ 80	20	8.3	9	4.6
Mean \pm SD	67.6 \pm 9.2		62.0 \pm 11.3	
Smoking habits				
Never smoked				
Ex-smokers (cigarette-years)				
0–399	13	5.4	52	26.4
400–799	12	5.0	12	6.1
800–1199	11	4.6	11	5.6
1200+	23	9.5	7	3.6
Current smokers (cigarette-years)				
0–399	13	5.4	16	8.1
400–799	28	11.6	29	14.7
800–1199	57	23.7	20	10.2
1200–1599	24	10.0	7	3.6
1600–1999	10	4.2	5	2.5
2000+	15	6.2	4	2.0
Unknown	4	1.7	24	12.2

power and 5% type I error, were 387, 80, 545, and 172 cases for total lung cancer, squamous cell carcinoma, adenocarcinoma, and nonadenocarcinoma, respectively, when the same number of cases and controls are recruited and the risk of *Cys/Cys* genotype *versus* other genotypes combined is evaluated.

Distribution in Different Populations. As shown in Table 4 all the distributions of this genotype in Japanese (Tokyo), Chinese (Jiangsu), Hungarian Caucasians, and Micronesians were consistent with Hardy-Weinberg equilibrium, but those of Melanesians ($P = 2.8 \times 10^{-5}$) and Australian Caucasians ($P = 0.002$) were not. The *Ser/Ser* genotype was less frequent in Chinese, whereas the prevalence of the *Cys/Cys* genotype was relatively low in Australian Caucasians, Melanesians, and Hungarians. A significant difference in genotype distributions was detected in these populations ($P = 6.4 \times 10^{-31}$).

Discussion

8-Hydroxyguanine is one of the most common form of DNA damage caused by oxidative DNA injury (26). The increase of 8-hydroxyguanine content in DNA has been shown to elevate cancer risk (27). The repair system for this damaged DNA in *E. coli* has been well characterized, and a human homologue of yeast *OGG1* was recently cloned (1–6). Genetic polymorphisms of *hOGG1* have been documented (10), and it is expected that they play a role in human cancer susceptibility.

We took advantage of a lung cancer case-control DNA set in Okinawa, which previously disclosed the *Cyp1A1* Ile-Val polymorphism as a possible high-risk marker for lung cancer (13). There are several pieces of evidence implicating oxyradical and subsequent 8-hydroxyguanine formation in human lung carcinogenesis (9, 28, 29). Therefore, the interindividual differences to repair these lesions may be associated with lung cancer susceptibility. Because the content of 8-hydroxyguanine is increased in smokers' leukocytes (26), this association is expected to be most noticeable with tobacco-related subtypes. In a bacterial complementation assay system, the *Ser* allele was

Table 2 ORs according to the *hOGG1* Ser326Cys polymorphism versus Ser/Ser genotype as a reference and those stratified by smoking dosage

Genotype	No. of cases/controls	Crude			Adjusted for age and smoking habits		
		OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Total							
<i>Ser/Ser</i>	85/63	1.00			1.00		
<i>Ser/Cys</i>	115/107	0.80	0.52–1.21	0.287	0.64	0.39–1.06	0.081
<i>Cys/Cys</i>	41/27	1.13	0.63–2.02	0.692	1.31	0.65–2.62	0.446
Squamous cell carcinoma							
<i>Ser/Ser</i>	40/63	1.00			1.00		
<i>Ser/Cys</i>	54/107	0.80	0.48–1.33	0.381	0.63	0.33–1.18	0.150
<i>Cys/Cys</i>	24/27	1.40	0.71–2.76	0.331	2.27	0.92–5.60	0.075
Small cell carcinoma							
<i>Ser/Ser</i>	11/63	1.00			1.00		
<i>Ser/Cys</i>	15/107	0.80	0.35–1.86	0.608	0.58	0.23–1.47	0.252
<i>Cys/Cys</i>	2/27	0.42	0.09–2.05	0.285	0.51	0.09–2.87	0.447
Adenocarcinoma							
<i>Ser/Ser</i>	25/63	1.00			1.00		
<i>Ser/Cys</i>	40/107	0.94	0.52–1.70	0.843	0.77	0.40–1.47	0.424
<i>Cys/Cys</i>	13/27	1.21	0.54–2.72	0.639	1.34	0.53–3.39	0.537
Nonadenocarcinoma							
<i>Ser/Ser</i>	57/63	1.00			1.00		
<i>Ser/Cys</i>	73/107	0.75	0.47–1.20	0.235	0.59	0.33–1.05	0.071
<i>Cys/Cys</i>	28/27	1.15	0.61–2.17	0.675	1.59	0.71–3.57	0.262
					Adjusted for age		
					OR	95% CI	<i>P</i>
Cigarette-years <800							
<i>Ser/Ser</i>	28/38	1.00			1.00		
<i>Ser/Cys</i>	34/62	0.74	0.39–1.42	0.368	0.74	0.38–1.43	0.362
<i>Cys/Cys</i>	16/20	1.09	0.48–2.46	0.844	0.97	0.42–2.25	0.943
Cigarette-years ≥800							
<i>Ser/Ser</i>	57/15	1.00			1.00		
<i>Ser/Cys</i>	81/34	0.63	0.31–1.26	0.188	0.63	0.31–1.26	0.190
<i>Cys/Cys</i>	25/4	1.65	0.50–5.46	0.416	1.73	0.52–5.77	0.376

~7 times more capable of complementing a repair-deficient strain than the *Cys* allele (11). Thus, we assigned the *Ser/Ser* genotype or *Ser/Ser* and *Ser/Cys* genotypes combined as reference groups (10), but we should be aware that there is no solid biological rationale for this assignment of *Ser/Ser* plus *Ser/Cys* as a reference at this moment.

Compared to the *Ser/Ser* genotype, the *Ser-Cys* polymorphism was not associated with an increased risk of lung cancer in any subtype (Table 2). However, when homozygous *Cys/Cys* were compared against the other genotypes combined, the increased risk was observed in squamous cell carcinoma and nonadenocarcinoma after adjustment for age and smoking habits (Table 3). We still do not have a convincing explanation for our finding that only *Cys/Cys* was a high-risk genotype. These observations can be interpreted in several ways. Although we do not yet have *in vitro* data, these results are consistent with a recessive, reduced repair activity of the *Cys* allele. The hypothesis that only homozygous status of *Cys* (alternatively, the *Ser* allele is dominant) influences individual repair activity would explain the observation. Considering the assumed strong relationship of oxyradicals in tobacco smoke to squamous cell carcinoma, our observation that the significant association was limited to squamous cell carcinoma may reflect *hOGG1* commitment in at least some of tobacco-related carcinogenesis. Consistent with this interpretation, the ORs for heavy smokers were higher (although not statistically significant) for all comparisons (Tables 2 and 3). Currently, other subtypes such as adenocarcinoma of the lung are also considered to be associated with smoking, although the relative risk was much lower than

in squamous cell and small cell carcinoma (30). To the best of our knowledge, the involvement of oxyradicals in carcinogenesis of different subtype of lung cancer has never been addressed, and this issue remains to be investigated.

Our data may imply that the association of this genotype and lung cancer should not, however, be overemphasized. The lack of association with small cell carcinoma may be due to the low statistical power concomitant with the small number of these cancers. Our power calculation showed that our study seems to have a sufficient power to detect the risk only in squamous cell and nonadenocarcinoma. *hOGG1* polymorphisms other than Ser326Cys may play a role, or the contribution of this gene to repair 8-hydroxyguanine may be small relative to other repair systems, such as the nucleotide excision repair system (31).

As far as we know, this is the first case-control study of *hOGG1* Ser326Cys polymorphism as it relates to human lung cancer, and the findings may be a local phenomenon restricted to Okinawan lung cancer. Further studies will be necessary to clarify the involvement of this gene in human lung carcinogenesis in general. It is possible that the Ser326Cys polymorphism may be involved greater to oxidative damage repair in the other organs, and thus, to carcinogenesis or other pathological conditions, such as carcinoma of the stomach (32, 33).

It is well known that candidate genetic markers responsible for cancer susceptibility sometimes vary in frequencies among populations. Thus, it is very important to know the basic prevalence in multiple populations to evaluate the significance of the genetic markers in cancer risk assessment (34). The

Table 3 ORs for the Cys/Cys genotype of *hOGG1* Ser326Cys polymorphism versus the other genotypes combined and those stratified by smoking dosage

Genotype	No. of cases/controls	Crude			Adjusted for age and smoking habits		
		OR	95% CI	P	OR	95% CI	P
Total							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	200/170	1.00			1.00		
<i>Cys/Cys</i>	41/27	1.29	0.76–2.19	0.343	1.71	0.92–3.19	0.091
Squamous cell carcinoma							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	94/170	1.00			1.00		
<i>Cys/Cys</i>	24/27	1.61	0.88–2.94	0.124	3.01	1.33–6.83	0.008 ^a
Small cell carcinoma							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	26/170	1.00			1.00		
<i>Cys/Cys</i>	2/27	0.48	0.11–2.16	0.342	0.72	0.14–3.66	0.691
Adenocarcinoma							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	65/170	1.00			1.00		
<i>Cys/Cys</i>	13/27	1.26	0.61–2.59	0.531	1.58	0.68–3.65	0.290
Nonadenocarcinoma							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	130/170	1.00			1.00		
<i>Cys/Cys</i>	28/27	1.36	0.76–2.41	0.300	2.18	1.05–4.54	0.037 ^a
					Adjusted for age		
					OR	95% CI	P
Cigarette-years <800							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	62/100	1.00			1.00		
<i>Cys/Cys</i>	16/20	1.29	0.62–2.68	0.494	1.16	0.55–2.46	0.697
Cigarette-years ≥800							
<i>Ser/Ser</i> + <i>Ser/Cys</i>	138/49	1.00			1.00		
<i>Cys/Cys</i>	25/4	2.22	0.74–6.70	0.157	2.33	0.77–7.09	0.137

^a P < 0.05.Table 4 Ser326Cys polymorphism of *hOGG1* gene in six different ethnic groups^a

Genotype	Chinese (Jiangsu)	Hungarian	Australian Caucasian	Japanese (Tokyo)	Melanesian (Vanuatu)	Micronesian (Yap)
<i>Ser/Ser</i>	12 (12.0)	95 (63.7)	55 (39.9)	26 (27.7)	41 (74.5)	41 (25.8)
<i>Ser/Cys</i>	53 (54.1)	50 (33.6)	78 (56.5)	54 (57.4)	12 (21.8)	105 (66.0)
<i>Cys/Cys</i>	33 (33.9)	4 (2.7)	5 (3.6)	14 (14.9)	2 (3.7)	13 (8.2)

^a Numbers in parenthesis are percentages.

distribution of the Ser326Cys polymorphism was significantly different among several ethnic groups. Further research on the importance of *hOGG1* gene in oxidative damage repair is needed to determine the applicability of the Ser326Cys polymorphism as a marker for increased cancer risk in light of the highly variable allele frequencies we have observed among populations. The differences of this polymorphism among populations will influence the interpretations and strategies for its use as a potential tool for estimation of a particular individual risk, as has been done for *CYP1A1* (34–37). In the populations that have low Cys allele frequencies, like the Hungarians, our power analysis indicated that required sample sizes needed to obtain significant results would be so large that such studies would not be economically feasible. Previously, we reported an association of *CYP1A1* Ile-Val polymorphism with lung cancer in this area and observed a significantly increased risk of Val/Val genotype for some of lung cancer (13). As far as the ORs are comparable (they would be comparable if the sample size was sufficiently large and CIs of the ORs were not so wide), the lung cancer risk associated with the Ser326Cys polymorphisms appears to be smaller than that associated with the Ile-Val polymorphism of *CYP1A1* (13).

In conclusion, the Ser-Cys *hOGG1* polymorphisms, especially the Cys/Cys genotype, has a potential role as a high risk

marker for at least a subset of tobacco-related lung cancer. We found increased ORs among Cys/Cys individuals with higher smoking dosage, consistent with the hypothesis that smoking induced 8-hydroxyguanine is repaired less in heavy smokers with this susceptible genotype, although the association was not statistically significant.

References

- Aburatani, H., Hippe, Y., Ishida, T., Takashima, R., Matsuba, C., Kodama, T., Takao, M., Yasui, A., Yamamoto, K., Asano, M., Fukasawa, K., Yoshinari, T., Inoue, H., Ohtsuka, E., and Nishimura, S. Cloning and characterization of mammalian 8-hydroxyguanine-specific DNA glycosylase/apurinic, apyrimidinic lyase, a functional mutM homologue. *Cancer Res.*, 57: 2151–2156, 1997.
- Arai, K., Morishita, K., Shinmura, K., Kohno, T., Kim, S. R., Nohmi, T., Taniwaki, M., Ohwada, S., and Yokota, J. Cloning of a human homolog of the yeast *OGG1* gene that is involved in the repair of oxidative DNA damage. *Oncogene*, 14: 2857–2861, 1997.
- Lu, R., Nash, H. M., and Verdine, G. L. A mammalian DNA repair enzyme that excises oxidatively damaged guanines maps to a locus frequently lost in lung cancer. *Curr. Biol.*, 7: 397–407, 1997.
- Radicella, J. P., Dherin, C., Desmaze, C., Fox, M. S., and Boiteux, S. Cloning and characterization of hOGG1, a human homolog of the *OGG1* gene of *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. USA*, 94: 8010–8015, 1997.
- Roldan-Arjona, T., Wei, Y. F., Carter, K. C., Klungland, A., Anselmino, C., Wang, R. P., Augustus, M., and Lindahl, T. Molecular cloning and functional

- expression of a human cDNA encoding the antimutator enzyme 8-hydroxyguanine-DNA glycosylase. *Proc. Natl. Acad. Sci. USA*, *94*: 8016–8020, 1997.
6. Rosenquist, T. A., Zharkov, D. O., and Grollman, A. P. Cloning and characterization of a mammalian 8-oxoguanine DNA glycosylase. *Proc. Natl. Acad. Sci. USA*, *94*: 7429–7434, 1997.
 7. Wang, Y. J., Ho, Y. S., Lo, M. J., and Lin, J. K. Oxidative modification of DNA bases in rat liver and lung during chemical carcinogenesis and aging. *Chem. Biol. Interact.*, *94*: 135–145, 1995.
 8. Nakae, D., Kobayashi, Y., Akai, H., Andoh, N., Satoh, H., Ohashi, K., Tsutsumi, M., and Konishi, Y. Involvement of 8-hydroxyguanine formation in the initiation of rat liver carcinogenesis by low dose levels of *N*-nitrosodiethylamine. *Cancer Res.*, *57*: 1281–1287, 1997.
 9. Inoue, M., Osaki, T., Noguchi, M., Hirohashi, S., Yasumoto, K., and Kasai, H. Lung cancer patients have increased 8-hydroxydeoxyguanosine levels in peripheral lung tissue DNA. *Jpn. J. Cancer Res.*, *89*: 691–695, 1998.
 10. Kohno, T., Shinmura, K., Tosaka, M., Tani, M., Kim, S-R., Sugimura, H., Nohmi, T., Kasai, H., and Yokota, J. Genetic polymorphisms and alternative splicing of the *hOGG1* gene, that is involved in the repair of 8-hydroxyguanine in damaged DNA. *Oncogene*, *16*: 3219–3226, 1998.
 11. Shinmura, K., Kasai, H., Sasaki, A., Sugimura, H., and Yokota, J. 8-Hydroxyguanine (7,8-dihydro-8-oxoguanine) DNA glycosylase and AP lyase activities of *hOGG1* protein and their substrate specificity. *Mutat. Res.*, *385*: 75–82, 1997.
 12. Ishida, T., Takashima, R., Fukayama, M., Hamada, C., Hippo, Y., Fujii, T., Moriyama, S., Matsuba, C., Nakahori, Y., Morita, H., Yazaki, Y., Kodama, T., Nishimura, S., and Aburatani, H. New DNA polymorphisms of human *MMH/OGG1* gene: prevalence of one polymorphism among lung-adenocarcinoma patients in Japanese. *Int. J. Cancer*, *80*: 18–21, 1999.
 13. Sugimura, H., Wakai, K., Genka, K., Nagura, K., Igarashi, H., Nagayama, K., Ohkawa, A., Baba, S., Morris, B. J., Tsugane, S., Ohno, Y., Gao, C. M., Li, Z. Y., Takezaki, T., Tajima, K., and Iwama, T. Association of Ile462Val (exon 7) polymorphism of cytochrome P450IA1 with lung cancer in the Asian population: further evidence from a case-control study in Okinawa. *Cancer Epidemiol. Biomark. Prev.*, *7*: 413–417, 1998.
 14. Shanmugaratnam, K., and Sobin, L. H. *Histological Typing of Upper Respiratory Tract Tumors. International Histological Classification of Tumors.* Geneva: WHO, 1978.
 15. Hasleton, P. S. *Spencer's Pathology of the Lung.* New York: McGraw-Hill, 1996.
 16. Ohno, Y., Wakai, K., Genka, K., Ohmine, K., Kawamura, T., Tamakoshi, A., Aoki, R., Senda, M., Hayashi, Y., Nagao, K., Fukuma, S., and Aoki, K. Tea consumption and lung cancer risk: a case-control study in Okinawa, Japan. *Jpn. J. Cancer Res.*, *86*: 1027–1034, 1995.
 17. Dobashi, Y., Sugimura, H., Sakamoto, A., Mernyei, M., Mori, M., Oyama, T., and Machinami, R. Stepwise participation of *p53* gene mutation during dedifferentiation of human thyroid carcinomas. *Diagn. Mol. Pathol.*, *3*: 9–14, 1994.
 18. Breslow, N. E., and Day, N. E. Unconditional logistic regression for large strata. *In: Statistical Methods in Cancer Research*, pp. 192–246. Lyon: IARC, 1980.
 19. Armitage, P., and Berry, G. Goodness of fit of frequency distributions. *In: P. Armitage and G. Berry (eds.), Statistical Methods in Medical Research*, pp. 394–399. Oxford: Blackwell Science Ltd., 1994.
 20. Schlesselman, J. J. Sample size requirements in cohort and case-control studies of disease. *Am. J. Epidemiol.*, *99*: 381–384, 1974.
 21. Csete, K., Schurenkamp, M., and Varga, T. The STR systems HumVWA and HumACTBP2 in a Hungarian population. *Int. J. Legal Med.*, *108*: 316–317, 1996.
 22. Lum, J. K., Cann, R. L., Martinson, J. J., and Jorde, L. B. Mitochondrial and nuclear genetic relationships among pacific island and asian populations. *Am. J. Hum. Genet.*, *63*: 613–624, 1998.
 23. Lum, J. K., and Cann, R. L. mtDNA and language support a common origin of Micronesians and Polynesians in Island Southeast Asia. *Am. J. Phys. Anthropol.*, *105*: 109–119, 1998.
 24. Sobue, T., Ajiki, W., Tsukuma, H., Oshima, A., Hanai, A., and Fujimoto, I. Trends of lung cancer incidence by histologic type: a population-based study in Osaka, Japan. *Jpn. J. Cancer Res.*, *90*: 6–15, 1999.
 25. Nakazato, I., Hirayasu, T., Kamada, Y., Tshahoko, K., and Iwamasa, T. Carcinoma of the lung in Okinawa, Japan: with special reference to squamous cell carcinoma and squamous metaplasia. *Pathol. Int.*, *47*: 659–672, 1997.
 26. Asami, S., Hirano, T., Yamaguchi, R., Tomioka, Y., Itoh, H., and Kasai, H. Increase of a type of oxidative DNA damage, 8-hydroxyguanine, and its repair activity in human leukocytes by cigarette smoking. *Cancer Res.*, *56*: 2546–2549, 1996.
 27. Greim, H., Csanady, G., Filser, J. G., Kreuzer, P., Schwarz, L., Wolff, T., and Werner, S. Biomarkers as tools in human health risk assessment. *Clin. Chem.*, *41*: 1804–1808, 1995.
 28. Asami, S., Manabe, H., Miyake, J., Tsurudome, Y., Hirano, T., Yamaguchi, R., Itoh, H., and Kasai, H. Cigarette smoking induces an increase in oxidative DNA damage, 8-hydroxydeoxyguanosine, in a central site of the human lung. *Carcinogenesis (Lond.)*, *18*: 1763–1766, 1997.
 29. Erhola, M., Toyokuni, S., Okada, K., Tanaka, T., Hiai, H., Ochi, H., Uchida, K., Osawa, T., Nieminen, M. M., Alho, H., and Kellokumpu-Lehtinen, P. Biomarker evidence of DNA oxidation in lung cancer patients: association of urinary 8-hydroxy-2'-deoxyguanosine excretion with radiotherapy, chemotherapy, and response to treatment. *FEBS Lett.*, *409*: 287–291, 1997.
 30. Barbone, F., Bovenzi, M., Cavallieri, F., and Stanta, G. Cigarette smoking and histologic type of lung cancer in men. *Chest*, *112*: 1474–1479, 1997.
 31. Reardon, J. T., Bessho, T., Kung, H. C., Bolton, P. H., and Sancar, A. *In vitro* repair of oxidative DNA damage by human nucleotide excision repair system: possible explanation for neurodegeneration in xeroderma pigmentosum patients. *Proc. Natl. Acad. Sci. USA*, *94*: 9463–9468, 1997.
 32. Correa, P., Miller, M., and Mannick, E. E. Oxidative damage during the gastric precancerous process. *In: E. Tahara (ed.), Molecular Pathology of Gastrointestinal Cancer, Application to Clinical Practice*, pp. 23–29. Tokyo: Springer-Verlag, 1997.
 33. Shinmura, K., Kohno, T., Kasai, H., Koda, K., Sugimura, H., and Yokota, J. Infrequent mutations of the *hOGG1* gene, that is involved in the excision of 8-hydroxyguanine in damaged DNA, in human gastric cancer. *Jpn. J. Cancer Res.*, *89*: 825–828, 1998.
 34. Garte, S. The role of ethnicity in cancer susceptibility gene polymorphisms: the example of CYP1A1. *Carcinogenesis (Lond.)*, *19*: 1329–1332, 1998.
 35. Sugimura, H., Suzuki, I., Hamada, G. S., Iwase, T., Takahashi, T., Nagura, K., Iwata, H., Watanabe, S., Kino, I., and Tsugane, S. Cytochrome P-450 IA1 genotype in lung cancer patients and controls in Rio de Janeiro, Brazil. *Cancer Epidemiol. Biomark. Prev.*, *3*: 145–148, 1994.
 36. Sugimura, H., Hamada, G. S., Suzuki, I., Iwase, T., Kiyokawa, E., Kino, I., and Tsugane, S. CYP1A1 and CYP2E1 polymorphism and lung cancer, case-control study in Rio de Janeiro, Brazil. *Pharmacogenetics*, *5*: S145–S148, 1995.
 37. Hamada, G. S., Sugimura, H., Suzuki, I., Nagura, K., Kiyokawa, E., Iwase, T., Tanaka, M., Takahashi, T., Watanabe, S., Kino, I., and Tsugane, S. The heme-binding region polymorphism of cytochrome P450IA1 (Cyp1A1), rather than the *RsaI* polymorphism of IIE1 (Cyp1E1), is associated with lung cancer in Rio de Janeiro. *Cancer Epidemiol. Biomark. Prev.*, *4*: 63–67, 1995.
 38. Chevillard, S., Radicella, J. P., Levalois, C., Lebeau, J., Poupon, M. F., Oudard, S., Dutrillaux, B., and Boiteux, S. Mutations in *OGG1*, a gene involved in the repair of oxidative DNA damage, are found in human lung and kidney tumours. *Oncogene*, *16*: 3083–3086, 1998.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

*h*OGG1 Ser326Cys Polymorphism and Lung Cancer Susceptibility

Haruhiko Sugimura, Takashi Kohno, Kenji Wakai, et al.

Cancer Epidemiol Biomarkers Prev 1999;8:669-674.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/8/8/669>

Cited articles This article cites 32 articles, 11 of which you can access for free at:
<http://cebp.aacrjournals.org/content/8/8/669.full#ref-list-1>

Citing articles This article has been cited by 23 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/8/8/669.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/8/8/669>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.