GENETIC POLYMORPHISM OF XENOBIOTIC METABOLIZING ENZYMES AMONG CHINESE LUNG CANCER PATIENTS

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Polymorphisms in xenobiotic metabolizing enzymes have been implicated in inter-individual and inter-ethnic differences in cancer susceptibility. Several studies have indicated an association between variant alleles of the human CYP1A1, CYP2E1 and GSTM1 genes and lung cancer. Activity of microsomal epoxide hydrolase (HYL1) has also been associated with lung cancer, and 2 variant alleles causing amino acid substitutions have been described. We have investigated genetic polymorphisms of the CYP1A1, CYP2E1, GSTM1 and HYL1 genes in 76 Chinese lung cancer patients and 122 healthy subjects. The allele frequency of the CYP1A1*2B allele was 0.21 among lung cancer patients and 0.20 in the reference group, whereas the corresponding values for the CYP1A1*2A allele were 0.34 and 0.36. The CYP2E1*5B and CYP2E1*6 alleles were less frequent among the cancer patients (0.20 and 0.22) compared with healthy subjects (0.25 and 0.26). The frequency distribution of the HYL1*2 allele was 0.49 among lung cancer patients and 0.42 in the reference group, and the corresponding frequencies for the HYL1*3 allele were 0.13 and 0.10. The homozygous GSTM1*0 genotype was found in 64% of lung cancer patients and in 66% of healthy subjects. Among heavy smokers, the frequency was 73%. The differences in the distribution of variant CYP1A1, CYP2E1 and GSTM1 alleles in lung cancer patients and healthy controls were not statistically significant. Our results indicate that the polymorphisms investigated are of minor importance as genetic susceptibility markers for lung cancer in this population. An increased risk for lung cancer in subjects carrying the HYL1*2 allele was observed and suggests that polymorphism in this gene might possibly be a susceptibility factor in the Chinese population. Int. J. Cancer 81:325–329, 1999.

Lung cancer incidence in the world is increasing, mainly due to the use of tobacco. In China, the frequency of cigarette and pipe smokers is high but the reported incidence of lung cancer is in general lower compared to Eastern and Western Europe and the United States. An exception is a high incidence of lung cancer, especially adenocarcinomas (ADs), among non-smoking Chinese women. In a study from Guandong, only 20% of the incidence of female lung cancer could be explained by smoking (Wang et al., 1996). The major risk factors identified in non-smoking Chinese women are a family history of lung cancer, cooking oil fume and indoor air pollution from burning coal. This suggests that both environmental and inherited factors are of importance in the etiology of lung cancer in China.

Genetic polymorphism of xenobiotic metabolizing enzymes might influence individual susceptibility to cancer. Variant alleles encoding proteins with different activity, substrate specificity or expression pattern may cause inter-individual differences in the capacity to detoxify or activate carcinogens. CYP1A1, CYP2E1, GSTM1 and microsomal epoxide hydrolase (HYL1) are enzymes expressed in the lung and presumably involved in the metabolism of carcinogens in cigarette smoke and pollutions. Studies investigating the association of polymorphisms in these genes and lung cancer susceptibility have been reviewed by Bartsch and Hietanen (1996). The CYP1A1*2A, *2B, *2C alleles and the GSTM1*0 genotype have been associated with increased lung cancer susceptibility in several Japanese studies, but studies in Caucasians show conflicting results (nomenclature suggested by Nebert et al., 1999). The CYP2E1*5B allele was also associated with increased lung cancer risk in a Japanese study, whereas among Mexican-Americans and in a Swedish population the same allele appears to have a protective effect (Oyama et al., 1997; Persson et al., 1993; Wu et al., 1998). The CYP2E1*6 allele, carrying an intron mutation, has been reported to be less frequent among both Japanese and African-American lung cancer patients (Batsch and Hietanen, 1996; Wu et al., 1998). Low HYL1 activity in lymphocytes has previously been observed in lung cancer patients (Heckbert et al., 1992). The HYL1*2 and *3 alleles encode proteins with altered stability; the association of these polymorphisms and lung cancer has not been extensively studied (Hassett et al., 1994 and references therein).

Studies in Japanese individuals, in general, have shown a stronger association between polymorphic alleles and lung cancer. A reason for this might be that the variant alleles, with the exception of the GSTM1*0 allele, are more frequent in this population compared with Western populations, and the statistical power in these studies, therefore, is stronger. Environmental risk factors specific for the Japanese may also play a role. Few studies have been published concerning the relationship between lung cancer and genetic polymorphisms among the Chinese population. Although the etiology of lung cancer among Chinese is less markedly associated with smoking, xenobiotic metabolizing enzymes such as CYP1A1, CYP2E1, GSTM1 and HYL1 might be important in relation to risk factors such as coal combustion, oil fumes and fried food. The expected frequencies of variant alleles among Chinese are similar to the frequencies observed among Japanese, which might make it easier to detect risk alleles.

In this study, we have investigated polymorphisms in CYP1A1, CYP2E1 and GSTM1 in 76 Chinese lung cancer patients and 122 healthy subjects. In contrast with studies among Japanese, we found no evidence that carriers of certain alleles have an increased risk of lung cancer. We also investigated the frequency of variant HYL1 alleles in the 2 groups. The heterozygous with HYL1*3 genotype was more frequent among cases than healthy subjects, which indicates that this might be an allele associated with increased lung cancer risk among Chinese.

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Study subjects

DNA from 76 Chinese lung cancer patients from Beijing was examined. Data on gender, age and diagnosis were collected, and the composition of the lung cancer group is presented in Table I. Among the lung cancer patients, 55.3% were males and 39.5% were below age 55 years at the time of diagnosis. Fifty percent of the patients were diagnosed with ADs. Information on smoking habits was available for 63% (48/76) of the cancer patients and revealed that 26% (20/76) had a history of smoking. The reference group consisted of 122 healthy, unrelated Chinese individuals, now living in Sweden. This study was approved by the Ethics Committee, Karolinska Institute.

Genotyping analyses

Nuclei from granulocytes were isolated and stored at −20°C until DNA isolation by chloroform and phenol extraction. The polymorphisms characteristic for the CYP1A1*2A and *2B alleles were analyzed by PCR methods previously described by Hayashi et al. (1991a). The GSTM1 polymorphism was detected with PCR essentially as described by Brockmoller et al. (1992). Lack of amplification with this method is indicative of homozygous deletion of GSTM1. Two β-actin primers (Stratagene, La Jolla, CA) were included in the PCR as a positive internal control, and the optimal reaction conditions for the 4 primers were established. PCR was performed on a Perkin-Elmer (Foster City, CA) Thermocycler 2400 under the following conditions: denaturation 94°C for 24 sec, annealing at 53°C during 45 sec and elongation at 73°C for 1 min, in 35 cycles. The PCR mix contained 0.16 µM of the GSTM1-specific primers, 0.06 µM of the β-actin primers and 1.5 mM of MgCl2. The results were analyzed on a 2% agarose gel.

Amplification by the GST primers yielded a 273 bp fragment, while the β-actin primers yielded a 661 bp fragment.

Analysis of the polymorphic site in the 5′-flanking region of CYP2E1*5B was performed by RsaI digestion of PCR products, as described elsewhere (Persson et al., 1993). The polymorphic site of CYP2E1*6 was analyzed with PCR and subsequent digestion with Dral as described by Hirvonen et al. (1993).

The prevalence of the HYL1*2 polymorphism was examined with a single-step, allele-specific PCR using primer ex3Rmut (5′-AGT CTT GAA GTG AGG GTA-3′) or ex3Rwt (5′-AGT CTT GAA GTG AGG GTA-3′) together with the allele-specific primer ex3Rwt (5′-AGT CTT GAA GTG AGG GTA-3′). PCR was performed for 30 cycles under the following conditions: denaturation at 94°C for 1 min, annealing at 58°C for 1 min and elongation at 72°C for 1 min. PCR was preceded by an initial denaturation step, 94°C for 1 min, and terminated with a final elongation step, 72°C for 7 min. The reaction mix contained 0.25 µM of each primer, 0.200 mM dNTP and 1.0 mM MgCl2. The results were examined on a 2% agarose gel. Amplification yields a fragment of 232 bp. Genotyping for the HYL1*3 polymorphism was carried out using RsaI RFLP according to Hassett et al. (1994).

Heat-stable DNA polymerase was purchased from Advanced Biotechnologies (Leatherhead, UK), and restriction enzymes were from Boehringer-Mannheim (Mannheim, Germany). All chemicals were of the highest quality and used according to the manufacturer’s recommendations.

Statistical analyses

The χ² test with Yates’ correction was used to compare the distribution of the different alleles in the groups. To estimate the odds ratio (OR), the method recommended by Lathrop (1983 and references therein) was used:

\[ \text{OR} = \frac{(a + 0.5)(d + 0.5)}{(b + 0.5)(c + 0.5)} \]

and the variance (V) was calculated as:

\[ V = \frac{1}{a + 1} + \frac{1}{b + 1} + \frac{1}{c + 1} + \frac{1}{d + 1} \]

where a and b are the number of subjects among patients and controls carrying the “susceptible” genotype, c and d are the corresponding numbers of subjects carrying the “non-susceptible” genotype and V is variance.

RESULTS

The methods used for genotyping do not determine whether different polymorphisms in the same gene are located on the same allele in heterozygous subjects. The genotypes will therefore be referred to the alleles, for which the single polymorphism is characteristic. The wild-type (wt) denotation refers to the wild-type genotype at a single polymorphic site.

The results of genotyping analyses are presented in Tables II to VII. The distribution of genotypes was generally in agreement with the Hardy-Weinberg equilibrium, calculated on the basis of the allele frequencies. Table II presents the genotype frequencies and Table III the frequencies of mutant alleles and the GSTM1*0*0 genotype among lung cancer patients and healthy subjects. The frequency of the different alleles and genotypes in subgroups of diagnosis was analyzed but did not differ significantly between the groups.

Comparisons of the distribution of CYP1A1 genotypes in lung cancer patients and the reference group revealed only small and non-significant differences. The frequencies of the CYP1A1*2A and *2B alleles were 0.34 and 0.21 in the lung cancer group compared with 0.36 and 0.20 in the reference group. All subjects homozygous for the CYP1A1*2B allele (11 subjects) were also homozygous for the CYP1A1*2A allele. Only minor differences in the distribution of the CYP1A1*2A and *2B alleles were found comparing male and female cancer patients (Table IV). The differences in CYP1A1 genotype distribution between the age groups and smokers and non-smokers were not statistically significant.

### Table I – Lung Cancer Diagnosis in Relation to Gender, Age and Smoking Habits

<table>
<thead>
<tr>
<th>Gender (mean age)</th>
<th>AD (n=38)</th>
<th>SC (n=18)</th>
<th>SQ (n=14)</th>
<th>SQAD (n=4)</th>
<th>PL (n=2)</th>
<th>Total (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 24 (50.5)</td>
<td>14 (52.6)</td>
<td>12 (55.6)</td>
<td>11 (62.0)</td>
<td>3 (62.7)</td>
<td>2 (58.5)</td>
<td>42</td>
</tr>
<tr>
<td>Female 24 (50.5)</td>
<td>14 (52.6)</td>
<td>12 (55.6)</td>
<td>11 (62.0)</td>
<td>3 (62.7)</td>
<td>2 (58.5)</td>
<td>42</td>
</tr>
<tr>
<td>Smoking 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (42)</td>
<td>18 (57)</td>
<td>11 (62.0)</td>
<td>3 (62.7)</td>
<td>2 (58.5)</td>
<td>42</td>
</tr>
<tr>
<td>1</td>
<td>2 (4)</td>
<td>3 (8.8)</td>
<td>1 (6.3)</td>
<td>1 (25)</td>
<td>1 (100)</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>1 (2)</td>
<td>3 (8.8)</td>
<td>1 (6.3)</td>
<td>1 (25)</td>
<td>1 (100)</td>
<td>9</td>
</tr>
<tr>
<td>ND*</td>
<td>14 (38)</td>
<td>8 (28)</td>
<td>11 (62.0)</td>
<td>3 (62.7)</td>
<td>2 (58.5)</td>
<td>42</td>
</tr>
</tbody>
</table>

1AD, adenocarcinoma; SC, small cell carcinoma; SQ, squamous cell carcinoma; SQAD, cancer of mixed appearance; PL, pleural carcinoma. 2Age at diagnosis (years). 3Pack/day * years of smoking. 4ND, no data available.
Table V shows the combined CYP2E1 genotypes among lung cancer patients and healthy subjects. The CYP2E1*5B and *6 alleles are in strong but not strict linkage disequilibrium in both groups. The frequency of the CYP2E1*5B allele was lower among cancer patients (0.20) and particularly infrequent among patients ≤55 years old (0.18) compared with healthy subjects (0.25), but the difference was not statistically significant (Tables III, IV). The frequency of the CYP2E1*6 allele was 0.22 among lung cancer patients compared with 0.26 in the reference population.

The frequency of the mutant allele HYLI*2 was 0.42 among healthy subjects and 0.49 among lung cancer patients. Among 20 lung cancer patients with a history of smoking, the frequency of the HYLI*2 allele was 0.60 [95% confidence interval (CI) 0.45–0.75]. The difference in allele frequency between smokers and non-smokers did not reach statistical significance.

The mutant HYLI*2 allele was found at an allele frequency of 0.13 among lung cancer patients and 0.10 in the reference group. The number of subjects heterozygous for the HYLI*3 allele was significantly higher ($p < 0.05$) than in the healthy subject group (Table II). However, no homozygous subject for this allele was found among the patients. One subject was homozygous for the HYLI*2 allele and heterozygous for the HYLI*3 allele, which demonstrates that the 2 mutant variants do occur on the same allele.

The method for the GSTM1 analysis differentiates between carriers and non-carriers of the GSTM1 gene but does not detect heterozygous subjects. The prevalence of individuals homozygous for the GSTM1*0*0 allele was 0.66 among healthy subjects and 0.64 in the cancer group. The distribution of the GSTM1*0*0 genotype among Chinese lung cancer patients and healthy subjects is shown in Table IV.
was higher among female (0.70) than among male (0.58) cancer patients. In patients <55 years old, the frequency was higher (0.70) than in patients ≥55 years old (0.60). Only a minor difference was found between smokers (0.65) and non-smokers (0.67), but in 20 patients with known smoking history, divided into heavy smokers (>25 packs/day * year) and light smokers ≤25, 73% of the heavy smokers and 56% of the light smokers carried the GST*0*0 genotype (Table VII).

The combined CYP1A1 and GSTM1 genotypes in cancer patients and healthy subjects are presented in Tables VI and VII. The distribution of the different genotypes agreed to a great extent with the expected values calculated from the allele frequencies, but among healthy controls the number of subjects homozygous for the CYP1A1*2B and the GSTM1*0*0 alleles were fewer (n = 1) than expected (n = 3.1). Among the lung cancer cases, 3 subjects with this genotype were observed compared with the expected, 2.1. The calculated OR for this genotype was 2.73 with a 95% CI of 0.45–16.71.

Subdivision of 20 smokers in the lung cancer group into heavy and light smokers did not reveal an increased risk for any of the groups determined by the combined CYP1A1wt and CYP1A1*2B alleles and the GSTM1 genotype (Table VII).

**DISCUSSION**

In our study, the frequency of variant CYP1A1, CYP2E1, GSTM1 and HYL1 alleles among Chinese lung cancer patients and the healthy subject group did not differ significantly. We were also unable to find significant differences in the allele frequencies comparing males and females, age groups, smokers and non-smokers or different diagnoses.

The frequency of cancer patients homozygous for the CYP1A1*2B allele was higher than that among healthy subjects, 8% vs. 4%, with a relative risk of 1.81 compared with the wt/wt genotype. However, if CYP1A1*2B was a true susceptibility gene, one would expect the frequency of the homozygous wt genotype to be lower among the cases. Here, the frequency of patients homozygous for the wt allele was higher than among the healthy subjects (0.66 vs. 0.65). The relative risk for subjects carrying 1 or 2 copies of the CYP1A1*2B allele was 0.96 (95% CI 0.53–1.74). This and the fact that the relative risk for the observed CYP1A1*2B/wt* genotype was not statistically significant suggests that CYP1A1*2B is not a susceptibility allele in this population. These results differ from what has been found in studies of the Japanese population but can be due to the large number of non-smokers in this study (Bartsch and Hietanen, 1996). However, the lowest frequency of the CYP1A1*2B allele was found among the smoking lung cancer patients.

The functional effects of the CYP1A1 polymorphisms have been investigated with some contradictory results. When expressed in yeast, the CYP1A1*1 and *2B variants exhibited only small differences in enzymatic properties (Persson et al., 1997). However, Kiyohara et al. (1998) showed increased, non-induced AH activity in mitogen-treated lymphocytes from Japanese subjects homozygous for the CYP1A1*2B allele and increased AH inducibility in subjects homozygous for the CYP1A1*2A allele. This implies that these polymorphisms might cause higher enzyme concentrations in vivo due to enhanced inducibility and increased enzyme stability.

The allele frequency and genotypes of the CYP2E1 gene did not differ significantly between lung cancer patients and healthy subjects. The alleles were in strong, but not strict, linkage disequilibrium, in contrast to what we found in a Swedish population, where the CYP2E1*5B- and CYP2E1*6-specific polymorphisms appeared to be in linkage disequilibrium (Persson et al., 1993). The CYP2E1*5B polymorphism has been found to affect transcription activity in vitro, while the CYP2E1*6 polymorphism is an intron mutation with no demonstrated functional effect (Hayashi et al., 1991b). A protective effect against lung cancer by the CYP2E1*5B allele was suggested in the Swedish study and among Mexican-Americans (Persson et al., 1993; Wu et al., 1998). Among Japanese, the frequency of the CYP2E1*5B*5B genotype was significantly higher than among controls in one study and the homozygous CYP2E1*6 genotype was associated with decreased susceptibility in other studies (Bartsch and Hietanen, 1996; Oyama et al., 1997). Differences between Japanese and Caucasians in CYP2E1-dependent metabolism have been measured both in vivo and in vitro in liver microsomes (Kim et al., 1996). The metabolism of chlorzoxazone was slower in Japanese, but no relation between CYP2E1-dependent activity and any of the polymorphisms was found. Since little is known about the expression of CYP2E1 in the lung and the effects of these polymorphisms, the relationship between CYP2E1 polymorphism and lung cancer remains unclear.

The 2 allelic variants of the HYL1 gene were associated with an increased relative risk for lung cancer in this study. Both the frequency of the HYL1*2 allele and the relative risk for subjects homozygous for the HYL1*2 allele were higher among cancer patients than among healthy subjects and particularly among smokers. In vitro results suggest that the Y113H substitution causes a 40% decrease in protein stability, and low HYL1 activity in human leukocytes has previously been associated with the occurrence of lung cancer (Hassett et al., 1994; Heckbert et al., 1992). In this study, subjects homozygous for the HYL1*3 allele had a 2-fold higher risk for lung cancer. Since the frequency of the allele was low and differed only slightly between cancer patients and healthy subjects, it might be more correct to calculate the relative risk for subjects carrying at least one copy of the allele. The relative risk for subjects carrying the allele was still increased (1.79) but not to a significant level (95% CI 0.9–3.56). The allele was more frequent among lung cancer patients with a history of smoking and patients >55 years old. After in vitro expression, the H139R substitution was found to result in enhanced protein stability (Hassett et al., 1994).

These results indicate a possible relationship between the 2 variant HYL1 alleles and lung cancer. Cigarette smoke, cooking oil fume and charcoal combustion, which are suggested risk factors in the Chinese population, are likely to contain compounds which can form reactive epoxides in the body. The capacity to metabolize these compounds might therefore influence lung cancer risk. More extensive studies on the effect of these polymorphisms in vivo must be performed to establish the biological basis for these observations. The amount of HYL1 in the lung has been reported to vary 10-fold between individuals, and this might be explained by polymorphisms like the ones investigated in our study or by polymorphisms detected in the 5'-flanking region of the HYL1 gene (Raaka et al., 1998).

**TABLE V – CYP2E1 WT*5B GENOTYPE VERSUS CYP2E1 WT*6 GENOTYPE**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Healthy subjects (n)</th>
<th>Lung cancer patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>wt/wt</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>wt/5B</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>5B/5B</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>wt/2B</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>2B/2B</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

1wt refers to wild-type genotype at the polymorphic site.2Number of subjects.

**TABLE VI – ODDS RATIO (OR) AND DISTRIBUTION OF CYP1A1 AND GSTM1 GENOTYPES IN CHINESE LUNG CANCER PATIENTS AND HEALTHY SUBJECTS**

<table>
<thead>
<tr>
<th>CYP1A1 genotype</th>
<th>GSTM1 genotype</th>
<th>Patients (n)</th>
<th>Healthy subjects (n)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>wy/wt</td>
<td>wy/wt</td>
<td>17 (0.23)</td>
<td>20 (0.17)</td>
<td>1</td>
</tr>
<tr>
<td>wy/5B</td>
<td>wy/5B</td>
<td>32 (0.43)</td>
<td>57 (0.48)</td>
<td>0.66 (0.31–1.42)</td>
</tr>
<tr>
<td>5B/5B</td>
<td>7 (0.09)</td>
<td>16 (0.13)</td>
<td>0.53 (0.19–1.52)</td>
<td></td>
</tr>
<tr>
<td>wy/2B</td>
<td>wy/2B</td>
<td>13 (0.17)</td>
<td>21 (0.18)</td>
<td>0.74 (0.29–1.84)</td>
</tr>
<tr>
<td>2B/2B</td>
<td>3 (0.04)</td>
<td>4 (0.03)</td>
<td>0.91 (0.21–3.91)</td>
<td></td>
</tr>
<tr>
<td>*2B/+2B</td>
<td>*2B/+2B</td>
<td>3 (0.04)</td>
<td>1 (0.01)</td>
<td>2.73 (0.45–16.71)</td>
</tr>
</tbody>
</table>

1Alleles without (wt) or with *(2B) the I462V polymorphism.2GSTM1*1*1 and GSTM1*1*0 (+), GSTM1*0*0 (–).3Number of subjects (frequency).
The GSTM1*0*0 genotype was equally frequent among lung cancer patients and healthy subjects, and the frequency did not differ significantly according to gender, age and smoking history. Sun et al. (1997) reported an increased risk for lung cancer in Chinese especially for small cell carcinoma (SC) and in subjects below 50 years. We also found a slightly increased frequency of GSTM1*0*0 subjects in the group of SC patients (13 of 18 SC patients, $f = 0.72$) and among lung cancer patients below 55 years ($f = 0.70$) compared with healthy subjects ($f = 0.65$), but these observations did not reach statistical significance.

When combined with the CYP1A1/wt/CYP1A2*2B genotypes, all genotypes except CYP1A1*2B*2B + GSTM1*0*0 were found to be at lower risk than the combined wt genotype (CYP1A1/wt/wt + GSTM1*1*1). The OR for the CYP1A1*2B*2B + GSTM1*0*0 genotype was 2.73 (95% CI 0.45–16.71). Lathrop (1983) has previously shown, using the expected number of subjects with the control group, after division into several small groups. The resulting risk estimate will have a smaller variance than the observed differences in allele frequency or genotype between the lung cancer group and the healthy subjects indicate that these polymorphisms constitute only a minor factor influencing lung cancer susceptibility in the Chinese population. The observed increased risk for lung cancer in subjects carrying variant alleles of HVI1 indicates that this gene might be a susceptibility factor and that both the polymorphisms investigated here and other polymorphisms which influence the individual capacity to metabolize epoxides will be of interest in future studies. Discrepancies between our results and those from other ethnic groups might be explained by geographical differences determining environmental risk factors, as well as by genetic differences.

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REFERENCES


