Impact of Multiple Alcohol Dehydrogenase Gene Polymorphisms on Risk of Upper Aerodigestive Tract Cancers in a Japanese Population

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Abstract

Alcohol intake is positively associated with the risk of upper aerodigestive tract (UAT) cancer. The genes that encode alcohol-metabolizing enzymes, primarily alcohol dehydrogenases (ADH) and aldehyde dehydrogenases (ALDH), are polymorphic. In Caucasians, significant associations between polymorphisms in ADH1B (rs1229984) and ADH1C (rs698 and rs1693482), and UAT cancer have been observed, despite strong linkage disequilibrium among them. Moreover, UAT cancer was significantly associated with rs1573496 in ADH7, and not with rs1984362 in ADH4. However, little evidence is available concerning ADH4 or ADH7 polymorphisms in Asian populations. We conducted a matched case-control study to clarify the role of ADH polymorphisms in a Japanese population. Cases and controls were 585 patients with UAT cancer and 1,170 noncancer outpatients. Genotyping for ADHs and ALDH2 was done using TaqMan assays. Associations between polymorphisms and UAT cancer were assessed by odds ratios and 95% confidence intervals using conditional logistic regression models that adjusted for age, sex, smoking, drinking, and ALDH2. Adjusted odds ratios were significant for rs4148887 and rs3805322 in ADH4, rs1229984 in ADH1B, rs698 and rs1693482 in ADH1C, and rs284787, rs1154460, and rs3737482 in ADH7. We also observed that ADH7 rs3737482 and ADH4 rs4148887 had independently and statistically significant effects on UAT cancer. The magnitude of effect of these ADH polymorphisms was greater in subjects who were heavy drinkers, heavy smokers, and had esophageal cancer. These findings show that multiple ADH gene polymorphisms were associated with UAT cancer in this Japanese population. Further studies in various ethnicities are required. (Cancer Epidemiol Biomarkers Prev 2009;18(11):3097–102)

Introduction

Alcohol consumption is one of the most important risk factors for upper aerodigestive tract (UAT) cancer (1). Acetaldehyde, an oxidative product of ethanol, is suspected to be a major carcinogen behind this association (2). In general, ethanol is oxidized to acetaldehyde by alcohol dehydrogenase enzymes (ADH), which is then further oxidized to acetate by aldehyde-dehydrogenase enzymes (ALDH), mainly ALDH2 (3). Because the genes that encode these representative ethanol-metabolizing enzymes contain polymorphisms that modulate individual differences in ethanol- and acetaldehyde-oxidizing capacity (4), they have been hypothesized to explain individual differences in UAT cancer susceptibility. Identification of differences among individuals in susceptibility to UAT cancer will help our understanding of the mechanisms of UAT carcinogenesis and assist in the development of tailored UAT cancer prevention strategies.

There are seven ADH genes, namely ADH5, ADH4, ADH6, ADH1A, ADH1B, ADH1C, and ADH7 (4). The association between polymorphisms in some of these ADH genes and UAT cancers has been investigated, although most studies have focused on ADH1B rs1229984 or ADH1C (rs698 and rs1693482; refs. 5-13). Results suggested that individuals carrying alleles conferring slow oxidizing capacity had higher risk of UAT cancers. The largest, most comprehensive epidemiologic study recently conducted in Europe showed that the effect of ADH1C rs1693482 and rs698 was independent of that of ADH1B rs1229984, despite strong linkage disequilibrium (LD) among them (14). This study also showed that UAT cancer...
was significantly associated with rs1573496 in ADH7 in Caucasians, and not with rs1984362 in ADH4 (14).

However, little evidence is available concerning ADH4 or ADH7 polymorphisms in Asian populations. ADH2 is monomorphic in Caucasians, whereas ADH2 polymorphism (Glu504Lys, rs671) is prevalent in East Asians (15, 16). Those with ALDH2 Lys allele (null type) have higher risk for UAT cancer than those with ALDH2 Glu allele due to the catalytic inactivity for acetaldehyde elimination (17, 18). Although polymorphisms between ADHs and ALDH2 were not in LD, ADHs and ALDH2 might affect each other through their function for acetaldehyde creation and elimination. Therefore, the association between ADHs and UAT cancer in Asians might be different from that in Caucasians.

We conducted a case-control study to clarify differences in the magnitude of effect of ADH4, ADH7, ADH1B, and ADH1C polymorphisms on UAT cancer in a Japanese population.

Materials and Methods

Subjects. The subjects were 585 patients with no prior history of cancer who were histologically diagnosed with UAT cancer (oral cavity and pharynx cancer in 217, larynx cancer in 103, and esophageal cancer in 265) between January 2001 and December 2005 at Aichi Cancer Center Hospital (ACCH). All of the subjects were recruited in the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center, as described elsewhere (19, 20). UAT cancer was defined according to the following codes of the International Classification of Diseases and Related Health Problems (ICD10): oral cavity and oropharynx (C00.3-C00.9, C01, C02.0-C02.4, C03, C04, C05.0-C05.2, C06, C09, C10), hypopharynx (C12, C13), oral cavity-oropharynx/hypopharynx not otherwise specified (C02.8, C02.9, C05.8, C05.9, C14), larynx (C32), and esophagus (C15). Malignant neoplasms of the salivary glands (C07, C08), nasopharynx (C11), nasol (C30), and paranasal (C31) were excluded as they have quite distinct etiologies. The controls were 1,170 first-visit outpatients at ACCH during the same period who were confirmed to have no cancer and no history of neoplasia. Noncancer status was confirmed by medical examinations including radiographic examinations. Those who suspected of having UAT cancer were examined by physical or endoscopic inspection. Radiographic examinations were carried out for subjects suspected of having cancer after inspection. Controls were selected randomly and frequency matched with group of age category (<40, 40-49, 50-59, 60-69, >70) and sex (male, female) at a case-control ratio of 1:2.

Genotyping of ADH4, ADH7, ADH1B, ADH1C, and ALDH2. For each subject, DNA was extracted from the buffy coat fraction with a DNA Blood mini kit (Qiagen) or BioRobot EZ1 and EZ1 DNA Blood 350 mL kit (Qiagen). Genotyping for ADH4 rs4148887, ADH4 rs3805322, ADH7 rs284787, ADH7 rs1154460, ADH7 rs3737482, ADH7 rs1573496, ADH1B rs1229984, ADH1C rs1693382, ADH1C rs698, and ALDH2 rs671 was based on TaqMan Assays (Applied Biosystems). We used tagSNPs for ADH4 and ADH7 on the basis that minor allele frequencies for significant loci identified by the European study (14) are markedly low in Japanese and limited evidence was available to date about functional significance of polymorphisms in ADH4/ADH7 genes. TagSNPs were selected as those satisfying a minor allele frequencies of over 20% and an R^2 of >0.8 in JPT using the tagSNP Picker function at the International HapMap Web site.

Assessment of Alcohol Intake and Smoking Exposure. Lifetime alcohol consumption of various common beverages (Japanese sake, beer, shochu, whiskey, and wine) was determined in terms of the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent. We asked about the amount consumed in terms of “go” (180 mL) of Japanese sake equivalent, which contains 23 g ethanol, one large bottle (720 mL) of beer, two shots (57 mL) of whisky, or two and a half glasses of wine (200 mL). One drink of “shochu” (distilled spirit), which contains 25% ethanol, was rated as 108 mL. In this analysis, we defined one unit of drink as a half go. Total alcohol consumption (grams per consumption) of Japanese sake, beer, shochu, whiskey, and wine was calculated for current and former regular drinkers, who were then categorized into the four levels of never drinker, moderate drinker, high-moderate drinker, and heavy drinker. Heavy drinking was defined as consumption on 5 d or more per week and four units (46 g ethanol) or more on each occasion; high-moderate drinking as consumption on 5 d or more per week and fewer than four units (46 g ethanol) on each occasion; moderate drinking as consumption on 4 d or fewer per week; and never drinking as never having drunk alcoholic beverages. Information on smoking status was obtained in the three categories of nonsmoker, former smoker, and current smoker, with former smokers defined as those who had quit smoking at least 1 y before the survey. Cumulative smoking dose was evaluated as pack-years (PY), the product of the number of packs consumed per day and the number of years of smoking.

Statistical Analysis. Associations between polymorphisms and UAT cancer were assessed by odds ratio (OR) and 95% confidence interval (CI) using conditional logistic regression models. P values for heterogeneity were assessed by adding interaction terms between each ADH locus and confounders in the models. ORs and 95% CIs were estimated for per-allele, dominant, and recessive models. Genotypes were included as scores. Potential confounders considered in the multivariate analyses were age as a continuous variable, sex (male, female), smoking (PY < 5; 5 < PY < 20; 20 < PY < 40; 40 < PY), alcohol consumption (never, moderate, high-moderate, heavy), and ALDH2 genotype (Glu/Glu, Glu/Lys, Lys/Lys or Glu/Glu, Glu/Lys and Lys/Lys).

We applied a retrospective profile-likelihood method (21, 22) in logistic regression to evaluate haplotype effects by using “haploReg” command (23). We constructed haplotypes by using unphased information of loci that were in LD (ADH4 rs4148887, ADH4 rs3805322, ADH1B rs1229984, ADH1C rs698, ADH1C rs1693382, and ADH7 rs284787) on chromosome 4. As ADH7 rs3737482 was not in LD with other loci, we put this locus as a covariate in the model with other potential confounders (smoking, alcohol consumption, and indicator variables for ALDH2 genotypes) considered in conditional logistic regression for individual loci analysis. We estimated ORs in log additive model for haplotypes of their frequencies over 0.001 (Supplementary Table S1) compared with the most
frequent haplotype (CGAAGT) as well as an OR for ADH7 rs3737482. Discrepancies between expected and observed genotype and allele frequencies in the controls were assessed by accordance with the Hardy-Weinberg equilibrium using the \( \chi^2 \) test.

Statistical analyses were done using STATA version 10 (Stata Corporation). A \( P \) value of <0.05 was considered statistically significant. LD estimates were calculated using Haploview.

## Results

Table 1 shows the characteristics of cases and controls. Alcohol consumption was more prevalent in the cases than in the matched controls. In addition, prevalence of current smoking and cumulative exposure to smoking was also more prevalent among cases than controls.

Table 2 shows the genotype distributions for ADH4, ADH1B, ADH1C, and ADH7 and their ORs and 95% CIs for UAT cancer. Genotype distributions of each locus among controls were accordant with the Hardy-Weinberg equilibrium. We genotyped ADH7 rs1573496 in 412 subjects in this study, and confirmed that all carried homozygous C-alleles. This locus was therefore excluded from further analysis. Adjusted per allele ORs were significant for rs4148887 and rs3805232 in ADH4, rs1229984 in ADH1B, rs698 and rs1693482 in ADH1C, and rs284787, rs1154460, and rs3737482 in ADH7. ADH4 and ADH1B polymorphisms consistently showed statistically significant associations in both dominant and recessive models, and we did not observe marked changes in the ORs. Although ADH7 polymorphisms showed similar OR trends in the dominant and recessive models, the ORs for rs1154460 in the dominant model and rs284787 in the recessive model were not statistically significant. In contrast, rs698 and rs1693482 in ADH1C showed nonsignificant associations in the dominant and recessive models.

### Table 1. Characteristics of the cases and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>487 (83.2)</td>
<td>974 (83.2)</td>
</tr>
<tr>
<td>Female</td>
<td>98 (16.8)</td>
<td>196 (16.8)</td>
</tr>
<tr>
<td>Age at interview (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>20 (3.4)</td>
<td>42 (3.6)</td>
</tr>
<tr>
<td>40-49</td>
<td>46 (7.9)</td>
<td>101 (8.6)</td>
</tr>
<tr>
<td>50-59</td>
<td>186 (31.8)</td>
<td>355 (30.3)</td>
</tr>
<tr>
<td>60-69</td>
<td>217 (37.1)</td>
<td>460 (39.3)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>116 (19.8)</td>
<td>212 (18.1)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>16 (2.7)</td>
<td>30 (2.5)</td>
</tr>
<tr>
<td>Former smoker*</td>
<td>161 (27.5)</td>
<td>381 (32.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>326 (55.7)</td>
<td>399 (34.1)</td>
</tr>
<tr>
<td>Cumulative smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PY &lt; 5</td>
<td>103 (17.6)</td>
<td>448 (38.3)</td>
</tr>
<tr>
<td>5 ≤ PY &lt; 20</td>
<td>67 (11.5)</td>
<td>164 (14.0)</td>
</tr>
<tr>
<td>20 ≤ PY &lt; 40</td>
<td>161 (27.5)</td>
<td>258 (22.1)</td>
</tr>
<tr>
<td>40 ≤ PY</td>
<td>249 (42.6)</td>
<td>288 (24.6)</td>
</tr>
<tr>
<td>Alcohol drinking*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>94 (16.1)</td>
<td>361 (30.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>89 (15.2)</td>
<td>332 (28.4)</td>
</tr>
<tr>
<td>High-moderate</td>
<td>134 (22.9)</td>
<td>287 (24.5)</td>
</tr>
<tr>
<td>Heavy</td>
<td>253 (43.2)</td>
<td>196 (16.8)</td>
</tr>
<tr>
<td>Cancer site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral/pharynx</td>
<td>217 (37.1)</td>
<td>460 (39.3)</td>
</tr>
<tr>
<td>Larynx</td>
<td>103 (17.6)</td>
<td>399 (34.1)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>265 (45.3)</td>
<td>212 (18.1)</td>
</tr>
</tbody>
</table>

* Former smoker was defined as those who quit smoking at least 1 y.

### Table 2. Genotype frequency and ORs for ADH4, ADH1B, ADH1C, and ADH7

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Location</th>
<th>SNP</th>
<th>Major/Minor allele</th>
<th>Genotyped counts</th>
<th>Allelic frequency</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH4</td>
<td>Chr 4</td>
<td>100274885</td>
<td>rs4148887</td>
<td>C/T</td>
<td>0.34</td>
<td>0.66</td>
<td>1.45 (1.23-1.72)</td>
</tr>
<tr>
<td>ADH4</td>
<td>Chr 4</td>
<td>100274885</td>
<td>rs3805232</td>
<td>C/T</td>
<td>0.46</td>
<td>0.54</td>
<td>1.37 (1.15-1.62)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>Chr 4</td>
<td>100456342</td>
<td>rs1229984</td>
<td>A/G</td>
<td>0.31</td>
<td>0.69</td>
<td>1.52 (1.18-1.97)</td>
</tr>
<tr>
<td>ADH1B</td>
<td>Chr 4</td>
<td>100456342</td>
<td>rs1229984</td>
<td>G/A</td>
<td>0.59</td>
<td>1.01</td>
<td>1.32 (0.98-1.76)</td>
</tr>
<tr>
<td>ADH1C</td>
<td>Chr 4</td>
<td>100579812</td>
<td>rs698</td>
<td>C/T</td>
<td>0.09</td>
<td>0.91</td>
<td>1.62 (1.19-2.21)</td>
</tr>
<tr>
<td>ADH1C</td>
<td>Chr 4</td>
<td>100579812</td>
<td>rs1693482</td>
<td>T/C</td>
<td>0.09</td>
<td>0.91</td>
<td>1.62 (1.19-2.21)</td>
</tr>
<tr>
<td>ADH7</td>
<td>Chr 4</td>
<td>100560646</td>
<td>rs1154460</td>
<td>G/A</td>
<td>0.42</td>
<td>0.58</td>
<td>1.37 (1.04-1.82)</td>
</tr>
<tr>
<td>ADH7</td>
<td>Chr 4</td>
<td>100560646</td>
<td>rs1154460</td>
<td>T/C</td>
<td>0.41</td>
<td>0.58</td>
<td>1.37 (1.04-1.82)</td>
</tr>
<tr>
<td>ADH7</td>
<td>Chr 4</td>
<td>100560646</td>
<td>rs3737482</td>
<td>T/C</td>
<td>0.09</td>
<td>0.91</td>
<td>1.62 (1.19-2.21)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, smoking status, drinking status, and ALDH2.
These loci showed the suggestive dominant impact of minor alleles.

We further evaluated these loci according to background factors (Supplementary Figs. S1-6; Fig. 1). The magnitude of effect for the ADH polymorphisms was more evident in subjects who were heavy drinkers and smokers with more PYs. 

P values for heterogeneity were statistically significant for drinking status in each locus, as were those for smoking status, except for rs698 and rs1693482 in ADH1C. All ADH polymorphisms genotyped in this study were significantly associated with ORs for esophageal cancer, whereas no significant associations were observed between any ADH polymorphism and larynx cancer. The magnitudes of effect for the ADH polymorphisms in subjects heterozygous for ALDH2 were larger than those for subjects with homozygous ALDH2 Glu alleles.

Figure 2 shows the LD of the ADH4, ADH1B, ADH1C, and ADH7 polymorphisms. Higher LD was found among ADH4, ADH1B, and ADH1C polymorphisms and rs284787 in ADH7 polymorphisms. Although rs1154460...
and rs3737482 in ADH7 had higher LD, these two single nucleotide polymorphisms (SNP) had lower LD with the other six SNPs in ADH4, ADH1B, ADH1C, and ADH7.

We further investigated haplotype effects to estimate independent effect of rs3737482 in ADH7. Supplementary Table S1 shows the estimated haplotypes and their frequencies. Considering haplotypes, rs3737482 in ADH7 had a significant and independent effect for UAT cancer (Table 3). We also examined whether each locus of ADH4 had an independent effect. Because polymorphisms in ADH4 were in LD with other neighboring loci, we evaluated the ORs in subjects with ADH1B homozygous major alleles. We found a significant effect of rs4148887 in ADH4 (OR, 1.50; 95% CI, 1.12-2.01; P = 0.007), whereas we observed marginally significant association with rs3805322 (OR, 1.28; 95% CI, 0.99-1.66; P = 0.057).

Discussion

In this study, we found that multiple ADH gene polymorphisms showed significant associations with UAT cancers. Moreover, rs3737482 in ADH7 and rs4148887 in ADH4 had a significant and independence effect on UAT cancers in this Japanese population.

We observed that ADH7 polymorphisms were significantly associated with UAT cancer in a Japanese population. Of interest, these loci were different from that reported by Hashibe et al. (14) in Caucasians, rs1573496. We observed rs1573496 was monomorphic in our population. It might suggest the possibility that the risk of UAT cancer is in fact affected by an unknown truly functional polymorphism in LD with both rs1573496 and those we found within ADH7. Moreover, we observed a significant association with ADH4 rs4148887, whereas the study in Caucasian did not found any significant locus in ADH4 (14). Different patterns of recombination across ethnicities might lead to the identification of different loci. The relatively small size of our study warrants the need for additional work in other Asian populations, which in turn more generally affirms the importance of cross-ethnic collaborations (24).

In this study, the impact of ADH polymorphism was stronger in heavy drinkers, heavy smokers, and subjects with the ALDH2 Glu/Lys genotype. These factors have common characteristics in terms of acetaldehyde exposure. High alcohol intake results in high acetaldehyde exposure; owing to their low catalytic activity in the elimination of acetaldehyde, subjects with the ALDH2 Glu/Lys genotype are thus exposed to high concentrations of acetaldehyde following alcohol consumption. Smoking increases acetaldehyde exposure via its effect of increasing salivary acetaldehyde levels after alcohol intake (25). Given these findings, our observation of the marked impact of multiple ADH polymorphisms in these subpopulations may suggest the central role of acetaldehyde.

A second interesting finding of this study was the difference in the magnitude of effect of ADH polymorphisms across cancer sites. In particular, the associations were stronger for esophageal than for other cancers. Hashibe et al. (14) reported a similar phenomenon for ADH1B rs1229984 and ADH7 rs1573496. A possible reason for the difference might be the sample size for each cancer site. Or the variability in various types of exposure might be another possible reason. To date, few studies have investigated these differences in multiple ADH loci, but a broader understanding in other populations would help elucidate mechanisms in the carcinogenesis of UAT cancer.

LD within the ADH gene polymorphisms was observed. Despite this strong LD, rs1229984 in ADH1B and rs1693482 in ADH1C showed a significant independent association with UAT cancer (14). In this study, we showed an independence of ADH7 rs3737482 as well as ADH4 rs4148887. This supports substantial contribution of ADH4 and ADH7 in addition to other ADHs in UAT cancer risk. Further studies in various populations are warranted.

Our study had several methodologic strengths. First, it was conducted in a single region in central Japan. Second, potential confounding by age and sex was adjusted for by matching of these factors. Lastly, given that our allele frequencies were comparable with those previously reported in public databases such as HapMap JPT (16), bias in the distribution of selected polymorphisms was negligible.

Several potential limitations of our study also warrant mention. One methodologic issue was the selection of the hospital-based noncancer patients as controls. However, because cases and controls were selected from the same hospital and almost all patients lived in the Tokai area of central Japan, the internal validity of this case-control study is likely to be acceptable. External validity has been confirmed in our previous study (26). In addition, to dilute any bias that might have resulted from the inclusion of a specific diagnostic group that is related to the exposure, we did not set eligibility criteria for control diseases. Second, the figures for self-reported life-style factors considered as potential confounders may be inaccurate. If present, however, any such misclassification would likely be nondifferential, and would likely underestimate the causal association. Lastly, the moderate number of cases indicates the need for replication of our findings in a larger study in a population with the same ethnicity.

In conclusion, we showed that multiple ADH gene polymorphisms are significantly associated with UAT cancer in this Japanese population. Given the effect of LD within the ADH gene cluster, the independence of these SNPs was found in the Japanese population. However, evaluation is required in further large-scale studies in other ethnicities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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