Risk of metachronous squamous cell carcinoma in the upper aerodigestive tract of Japanese alcoholic men with esophageal squamous cell carcinoma: a long-term endoscopic follow-up study

Akira Yokoyama,1,5 Tai Omori,2 Tetsuji Yokoyama,3 Yasuo Sato,4 Hirofumi Kawakubo2 and Katsuya Maruyama1

1National Hospital Organization Kurihama Alcoholism Center, 5-3-1 Nobi, Yokosuka, Kanagawa 239-0841; Departments of 2Surgery and 4Otorhinolaryngology, Kawasaki Municipal Hospital, 12-1 Shinkawadori, Kawasaki, Kanagawa 210-0013; 3Department of Technology Assessment and Biostatistics, National Institute of Public Health, 2-3-6 Minami, Wako, Saitama 351-0104, Japan

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Screening of Japanese alcoholic men by endoscopy combined with oropharyngolaryngeal inspection and esophageal iodine staining has revealed a very high prevalence of squamous cell carcinoma (SCC) in the upper aerodigestive tract (UADT).1) We have reported findings that inactive heterozygous aldehyde dehydrogenase-2 (ALDH2) encoded by ALDH2*1/*2 (2–6) and the development of squamous cell carcinoma (SCC), especially multiple SCC, of the upper aerodigestive tract (UADT). This study aimed to identify determinants of the development of metachronous SCC in the UADT in alcoholics with esophageal SCC. Follow-up endoscopic examinations were carried out 4–160 months (median, 41 months) after initial diagnosis in 110 Japanese alcoholic men with esophageal SCC diagnosed by screening using endoscopy combined with oropharyngolaryngeal inspection and esophageal iodine staining. ALDH2*1/*2 was significantly associated with the presence of multiple primary intraesophageal SCC at the time of initial diagnosis. Metachronous primary SCC of the esophagus was diagnosed in 29 of the 81 patients whose initial esophageal SCC was treated by endoscopic mucosal resection alone, and metachronous primary SCC of the oropharyngolarynx was diagnosed in 23 of the 99 patients without synchronous primary SCC of the oropharyngolarynx at the time of initial diagnosis. The risks of metachronous esophageal SCC and oropharyngolaryngeal SCC were significantly higher in ALDH2*1/*2 heterozygotes than in ALDH2*1/*1 homozygotes (age-adjusted and alcohol-adjusted hazard ratio = 3.38 [95% confidence interval: 1.45–7.85] and 4.27 [1.42–12.89], respectively), and in patients with multiple primary intraesophageal SCC at the time of initial diagnosis than in patients with a solitary intraesophageal SCC (3.09 [1.41–6.78] and 3.25 [1.41–7.47], respectively). ALDH2*1/*2 and multiple synchronous intraesophageal SCC were found to be predictors of metachronous SCC in the UADT in this population. (Cancer Sci 2008; 99: 1164–1171)

Epidemiology, and End Results Program has reported a low frequency of synchronous (2%) and metachronous (3%) multiple cancers in patients with esophageal cancer during the period 1973–2003.2) The increase in Japan might be partly explained by a dramatic increase in the proportion of heavy drinkers who are heterozygous for inactive ALDH2. In 1979, only 3% of Japanese alcoholics had inactive heterozygous ALDH2, compared to 8% in 1986, and 13% in 1992.3) Inactive heterozygous ALDH2 has been consistently associated with cancer multiplicity in Japanese patients with SCC in the UADT.4–15) The International Agency for Research on Cancer has recently concluded that substantial mechanistic evidence in humans with ALDH deficiency indicates that acetaldehyde derived from the metabolism of ethanol in alcoholic beverages contributes to causing malignant esophageal tumors.16) Acetaldehyde could act as a carcinogen on the entire epithelium of the UADT and induce multiple independent malignant foci in the UADT.

The majority of cancerous esophageal lesions detected in our screening program were treated by endoscopic mucosal resection (EMR) in accordance with established criteria.1,17) and follow-up endoscopic examinations allowed us to observe the extremely high rate of development of metachronous primary SCC in the preserved esophagus and oropharyngolarynx. The aim of this study was to identify determinants of the development of metachronous SCC in the UADT in alcoholics with esophageal SCC by means of a long-term endoscopic follow-up study.

Materials and Methods

Patients. A total of 2953 Japanese alcoholic men (≥ 40 years old) with no history of gastrectomy or cancer in the UADT or stomach were screened using endoscopy combined with oropharyngolaryngeal inspection and esophageal iodine staining between January 1993 and December 2002 at the National Hospital Organization Kurihama Alcoholism Center. The screening detected esophageal SCC in 135 patients. The esophageal SCC of 125 of the 135 patients was treated at Kurihama Alcoholism Center, Ichikawa General Hospital, or Kawasaki Municipal Hospital by the authors, and the other 10 patients were referred to other hospitals. As of April 2007, two of the authors (A.Y. and T.O.) had carried out follow-up endoscopic examinations ranging from 4 to 160 months (median, 41 months) after the initial diagnosis of esophageal SCC in 110 of the 125 patients (56.7 ± 6.4 years old), but we

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failed to follow-up the other 15 patients for more than 2 months. The 110 patients were evaluated as the subjects of this study.

Follow-up endoscopy. The follow-up plan was to examine the patients by endoscopy combined with oropharyngolaryngeal inspection and esophageal iodine staining every 6 months, and the examinations were carried out with Olympus endoscopes (models Q10, P20, XQ200, XQ230, Q240, and Q240Z, in chronological order of use; Olympus Optical, Tokyo, Japan).

Multiple primary SCC in the UADT. The diagnosis of multiple primary SCC of the UADT was based on the results of an endoscopic examination and histological evaluation. We used the following criteria proposed by Kuwano et al.:(19) (i) each cancerous lesion showed definite features of malignancy and was localized without continuity with the other; and (ii) each carcinoma was accompanied by areas of intraepithelial carcinoma.

Drinking and smoking habits. All of the participants in this study were former smokers or had never smoked. We asked the criteria for alcohol dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised. Information on the patients’ drinking profiles and smoking habits was obtained from the patients and, when available, from significant others. Daily alcohol consumption during the preceding year was expressed in grams of ethanol per day calculated by means of a standard conversion table for alcoholic beverages. Beer was assumed to be 5% ethanol (v/v); wine, 12%; sake, 16%; shochu, 25%; and whiskey, 40%.

Flushing questionnaire. We uniformly interviewed 106 of the 110 patients by asking two simple questions about flushing:(21,22) (a) Do you always flush in the face immediately after drinking a glass of beer (yes or no)? And (b) did you always flush in the face immediately after drinking a glass of beer during the first second year after you started drinking (yes or no)? The designation ‘current flushing’ was applied to individuals who answered ‘yes’ to question (a) and ‘former flushing’ to those who answered ‘no’ to question (a) and ‘yes’ to question (b). The remaining subjects were classified as ‘never flushing’. Current or former flushing individuals were assumed to have inactive ALDH2.

BMI. On their initial visit to the Center, each patient’s body height was measured without shoes, and they were weighed wearing light clothing. The patients were classified into quartiles according to their BMI values.

Blood testing. During each patient’s initial visit to the Center for the evaluation of alcoholism we measured MCV by the electrical impedance method with an autoanalyzer (CELL-DYN 3500; Abbott, North Chicago, IL). MCV was measured in 80 patients within 7 days of their last drink. We then dichotomized them into an MCV <106 fl group and an MCV ≥106 fl group, because macrocytosis with an MCV value ≥106 fl within 7 days of taking their last alcoholic drink was found to be associated with an increased risk of esophageal SCC in our previous case–control study in Japanese alcoholic men.(49)

ALDH2 and ADH1B genotyping. Polymerase chain reaction–restriction fragment length polymorphism methods were used for ALDH2(23) and ADH1B(24) genotyping of lymphocyte DNA samples from all patients. To confirm the accuracy of genotyping

### Table 1. Basic characteristics of esophageal squamous cell carcinoma (SCC) patients at baseline (n = 110)

| Depth of esophageal SCC | n   | %  |
|-------------------------|-----|----|
| Epithelium              | 48  | 43.6|
| Mucosa                  | 27  | 24.5|
| Muscularis mucosa       | 14  | 12.7|
| Submucosa               | 17  | 15.5|
| Proper muscle layer or deeper | 4  | 3.6|

| Treatment                           | n   | %  |
|-------------------------------------|-----|----|
| EMR alone                           | 81  | 73.6|
| EMR and chemo/radiation therapy     | 12  | 10.9|
| Radical surgery                     | 12  | 10.9|
| Chemo/radiation therapy alone       | 5   | 4.5 |
| Multiple intraesophageal SCC        | 34  | 30.9|

| Synchronous oropharyngolaryngeal SCC | n   | %  |
|-------------------------------------|-----|----|
| Oral cavity/oropharyngeal           | 5   | 4.5 |
| Hypopharyngeal/epilaryngeal        | 5   | 4.5 |
| Both oral cavity/oropharyngeal and hypopharyngeal/epilaryngeal | 1  | 0.9 |

| Age (years)                          | n   | %  |
|--------------------------------------|-----|----|
| Median (Q1, Q3)                      | 5.0 | (3.5, 6.0) |

| Cigarette smoking (cigarettes/day)    | n   | %  |
|--------------------------------------|-----|----|
| <20                                  | 41  | 37.3|
| 20–29                                | 31  | 28.2|
| 30+                                  | 38  | 34.5|

| ALDH2 genotype                      | n   | %  |
|--------------------------------------|-----|----|
| *1/*1                                | 50  | 45.5|
| *1/*2                                | 60  | 54.5|
| *2/*2                                | 0   | 0   |

| ADH1B genotype                      | n   | %  |
|-------------------------------------|-----|----|
| *1/*1                                | 47  | 42.7|
| *1/*2                                | 25  | 22.7|
| *2/*2                                | 38  | 34.5|

| Alcohol flushing (n = 106)           | n   | %  |
|--------------------------------------|-----|----|
| Current                              | 7   | 6.6 |
| Former                               | 40  | 37.7|
| Never                                | 59  | 55.7|

| MCV (≥7 days after the last drink, n = 80) | n   | %  |
|--------------------------------------------|-----|----|
| Mean ± SD                                  | 103.4 ± 9.1 | NA
| ≥106 fl group,                              | 37  | 46.3|

*Two patients had primary cancers of the esophagus, oropharyngolarynx, and stomach. 1 unit = 22 g ethanol. 2 Alcohol flushing was classified on the basis of the results of an alcohol flushing questionnaire. ADH1B, alcohol dehydrogenase-1B; ALDH2, aldehyde dehydrogenase-2; EMR, endoscopic mucosal resection; fl, femtoliters; MCV, mean corpuscular volume; NA, not applicable; Q1, 25th percentile; Q3, 75th percentile; SD, standard deviation.
assignment, clear digestion patterns were used to determine the genotypes of all samples, and ALDH2 genotyping of each sample was carried out at least twice. Genotypes were determined without knowledge of the subjects’ status.

**Statistical analysis.** Data are expressed as the mean ± SD, percentiles, or percentage. The cumulative percentages of patients with metachronous cancer in the UADT were calculated according to the Kaplan–Meier method, and groups were compared by the log–rank test. The Cox proportional hazards model was used to estimate the hazard ratio and 95% confidence interval (CI) after adjustment for confounding factors. Independent risk factors were selected by the stepwise procedure with $P < 0.10$ for entry and removal. Age and alcohol drinking were forced into the model. Logistic regression analysis was used to compare categorical data between groups after adjustment for confounding factors, and the strength of associations was expressed as an odds ratio (OR) and 95% CI. All analyses were carried out using the SAS statistical package (version 9.1; SAS Institute, Cary, NC).

**Results**

Table 2 shows the number and depth of invasion of metachronous primary SCC in the UADT. Follow-up endoscopy resulted in a diagnosis of metachronous primary esophageal SCC in 29 of the 81 patients whose initial esophageal SCC was treated by EMR alone. Metachronous SCC in the oral cavity/oropharynx was diagnosed in 19 of the 104 patients without SCC in the sites at the time of the initial diagnosis, metachronous SCC in the hypopharynx/epilarynx in 13 of 104, and metachronous SCC in the endolarynx in 2 of 110. Ten of the patients had metachronous SCC in both the oral cavity/oropharynx and hypopharynx/epilarynx, and another patient with synchronous hypopharyngeal/epilaryngeal SCC had metachronous oral cavity/oropharyngeal SCC.

Thus, metachronous SCC in the oropharyngolarynx as a whole was diagnosed in 23 of the 99 patients without synchronous oropharyngolaryngeal SCC.

Table 2. Metachronous primary squamous cell carcinoma (SCC) in the upper aerodigestive tract of Japanese alcoholic men with esophageal SCC

| Metachronous SCC | Esophagus | Oral cavity/oropharynx | Hypopharynx/epilarynx | Endolarynx |
|------------------|-----------|------------------------|-----------------------|------------|
| Subjects at baseline (n) | 81 | 104 | 104 | 110 |
| Events during follow-up (n) | 29 | 19 | 13 | 2 |
| Cancer depth | | | | |
| Intramural | 20 | 8 | 5 | 1 |
| Muscularis mucosae (subepithelium‘) | 8 | 6 | 7 | 1 |
| Submucosa | 1 | 0 | 0 | 0 |
| Proper muscle layer or deeper | 0 | 5 | 1 | 0 |

‘Oropharyngolarynx lacks the muscularis mucosae.

Fig. 1. Flow diagram tracking the numbers of participants in this study, detailing the subsets of subjects who were used for different analyses. EMR, endoscopic mucosal resection; SCC, squamous cell carcinoma.
hypopharynx/epilarynx, and oropharyngolarynx as a whole (Table 4) were 3.38 (95% CI: 1.45–7.85), 2.53 (0.82–7.86), 12.08 (1.52–95.89), and 4.27 (1.42–12.89), respectively, in ALDH2*1/*2 heterozygotes in comparison with ALDH2*1/*1 homozygotes; and 3.09 (1.41–6.78), 2.41 (0.96–6.05), 3.73 (1.22–11.41), and 3.25 (1.41–7.47) in patients with multiple intraesophageal SCC at the baseline compared to those without it. The adjusted hazard ratio for SCC of the esophagus was 2.90 (1.35–6.22) in the patients with current/former flushing compared with those who had never experienced flushing. None of the other factors evaluated in the present study affected the risk of metachronous SCC in the UADT when adjusted for age and alcohol drinking. A multivariate stepwise analysis showed that ALDH2*1/*2 genotype and multiple intraesophageal SCC at the baseline were independent risk factors for metachronous SCC in the esophagus, and that cigarette smoking and multiple

Table 3. Relationship between aldehyde dehydrogenase-2 (ALDH2) genotype and number of multiple intraesophageal squamous cell carcinomas (SCC) at the baseline in 110 Japanese alcoholic men

| No. of multiple intraesophageal SCC at the baseline | n  | ALDH2*1/*2 genotype |
|---------------------------------------------------|----|---------------------|
|                                                   |   | Prevalence, n (%)   | Adjusted OR† 95% CI |
| 1                                                 | 76 | 34 (44.7)           | 1 Referent |
| 2                                                 | 20 | 15 (75.0)           | 3.68 (1.17–11.57) |
| 3+                                                | 14 | 11 (78.6)           | 4.73 (1.15–19.47) |
| Total                                             | 110| 60 (54.5)           | P = 0.006 for trend |

†Adjusted for age, amount of alcohol consumed, and number of cigarettes smoked, according to the logistic regression model. CI, confidence interval; OR, odds ratio.
intraesophageal SCC at the time of the baseline were independent risk factors for metachronous SCC in the oropharyngolarynx as a whole (Table 4, bottom).

Discussion

The results of this endoscopic follow-up study of Japanese alcoholic men with esophageal SCC showed very high prevalences of metachronous cancer in the UADT, that is, the cumulative rate for cancer in the oropharyngolarynx within 5 years were estimated as 39% in this alcoholic population, compared to 7% reported in a Japanese study of general patients after surgery for esophageal SCC.\(^{(25)}\) The metachronous cancers tended to occur in several organs in the same alcoholic patients, suggesting a common strong genetic and environmental etiology of these cancers. Our previous short-term follow-up study after EMR of esophageal SCC showed a high prevalence of metachronous esophageal SCC among alcoholic men with \(ALDH2^{*1/*2}\) and with synchronous multiple intraesophageal SCC,\(^{(5)}\) and these findings were confirmed in this long-term follow-up study. The present study showed that the associated risks of \(ALDH2^{*1/*2}\) and esophageal cancer multiplicity extended to a risk of metachronous SCC in both the oropharyngolarynx as a whole and the hypopharynx/epilarynx in particular. \(ALDH2^{*1/*2}\) has been consistently shown to be a strong risk factor for cancer multiplicity in Japanese patients with SCC in the UADT.\(^{(5,11–14)}\) The results of the present study showed a positive association between \(ALDH2^{*1/*2}\) and the number of intraesophageal SCC at baseline. The presence of multiple areas of esophageal dysplasia, which is also associated with \(ALDH2^{*1/*2},\)^{13,15} has been shown to increase the risk of metachronous SCC in the UADT in other follow-up studies of Japanese patients after EMR for esophageal SCC.\(^{(26,27)}\) All of these findings suggest that \(ALDH2^{*1/*2}\) plays a crucial role in multicentric or field cancerization throughout the entire mucosal surface of the UADT.

Individuals with inactive ALDH2 are incapable of rapidly eliminating acetaldehyde after consuming ethanol. Acetaldehyde has been established as a carcinogen in experimental animals,\(^{(28)}\) and is suspected of playing a critical role in carcinogenesis in humans.\(^{(16)}\) Higher levels of mutagenic acetaldehyde-derived DNA adducts have recently been shown in Japanese alcoholics.
with inactive ALDH2 compared with active ALDH2. Very high salivary acetaldehyde levels have also been shown in alcoholics, and they were found to be partly attributable to increased salivary acetaldehyde production as a result of oral microorganism overgrowth in addition to heavy alcohol consumption. After a moderate oral dose of alcohol the salivary acetaldehyde levels of persons with inactive ALDH2 are two to three times higher than those of persons with active ALDH2. Inefficient degradation of the acetaldehyde in inactive ALDH2 heterozygotes might result in a very high level of accumulation in the mucosa of the UADT after a high level of exposure to acetaldehyde, because ALDH2 expression in the UADT is extremely weak, if present at all. Thus it is reasonable to speculate that the high risk of metachronous SCC in the UADT in persons with inactive ALDH2 is the consequence of repeated high exposure of the UADT to acetaldehyde.

Although high acetaldehyde exposure due to ALDH2*1/*2 contributes to the development of synchronous multiple intraesophageal SCC, a multivariate analysis showed that the presence of the multiple intraesophageal SCC and ALDH2*1/*2 independently increased the risk of metachronous intraesophageal SCC after EMR for the initial esophageal SCC, and an analysis by the stepwise procedure showed a predominant effect of multiple intraesophageal SCC over ALDH2*1/*2 in increasing the risk of metachronous SCC in the oropharyngolarynx as a whole. Other factors associated with the presence of multiple intraesophageal SCC in alcoholics’ lifestyle or in their hereditary traits might also be associated with a higher risk of metachronous SCC in the UADT.

ALDH2*1/*2 and the initial multiplicity of intraesophageal SCC increased the risk of metachronous hypopharyngeal/epipharyngeal SCC (hazard ratios = 12.08 and 3.73, respectively), but the positive associations for oral cavity/oropharyngeal SCC did not reach the level of significance (hazard ratios = 2.53 and 2.41, respectively). However, 10 of the 13 hypopharyngeal/epipharyngeal SCC patients also had metachronous SCC in the oral cavity/oropharynx, and all 10 patients had ALDH2*1/*2. Previous case–control studies of Japanese alcoholics have shown similarly strong associations between ALDH2*1/*2 and both oral cavity/oropharyngeal SCC and hypopharyngeal/epipharyngeal SCC. However, the site-specific difference observed is consistent with the results of previous Japanese case–control studies of oral and pharyngeal SCC conducted in a general population. The mechanisms of metachronous carcinogenesis might differ among anatomically different sites.

Less-active ADH1B*1/*1, MCV ≥ 106 fl, and low BMI are independent risk factors for SCC in the UADT in Japanese alcoholic men, but none of them were associated with an increased risk of metachronous cancer development among the alcoholics with esophageal SCC. Ethanol and acetaldehyde persist in the saliva for longer periods in alcoholics with less-active ADH1B*1/*1 than in alcoholics with other genotypes. Macrocystosis in alcoholics has many causes, including heavy drinking, acetaldehyde exposure, aging, smoking, and poor nutritional status. Alcoholics’ low BMI is probably attributable to poor dietary habits that lead to vitamin deficiencies and suppressed immune function. A very high level of exposure of the UADT to acetaldehyde in persons with ALDH2*1/*2 could affect the risk of metachronous SCC in the UADT in a different manner from factors associated with less-active ADH1B*1/*1, MCV ≥ 106 fl, and low BMI. Our previous studies of Japanese alcoholics have also shown that the magnitude of the increase in risk of UADT cancer as a result of having inactive ALDH2*1/*2 was much greater than the increase in risk due to the less-active ADH1B*1/*1, MCV ≥ 106 fl, and low BMI and that, of the three factors of inactive ALDH2*1/*2, less-active ADH1B*1/*1, and MCV ≥ 106 fl, only inactive ALDH2*1/*2 was linked to synchronous multiplicity of UADT cancer in Japanese alcoholics with esophageal SCC. This finding is mainly explained by the

### Table 4. Risk factors for metachronous primary squamous cell carcinoma (SCC) in the upper aerodigestive tract of Japanese alcoholic men with esophageal SCC

| Risk factors                                      | Metachronous primary SCC |
|--------------------------------------------------|--------------------------|
|                                                   | Esophagus (29 cancers in 81 patients) | Oral cavity/oropharynx (19 cancers in 104 patients) | Hypopharynx/epipharynx (13 cancers in 104 patients) | Oropharyngolarynx as a whole (23 cancers in 99 patients) |
|                                                   | HR 95% CI                 | HR 95% CI                  | HR 95% CI                  | HR 95% CI                  |
| **Adjusted for age and alcohol consumption**      |                          |                          |                            |                            |
| ALDH2*1/*2 versus *1/*1                          | 3.38 (1.45–7.85)         | 2.53 (0.82–7.86)          | 12.08 (1.52–95.89)         | 4.27 (1.42–12.89)          |
| ALDH2*1/*1 plus *1/*2                            | 0.85 (0.38–1.88)         | 0.52 (0.20–1.38)          | 2.39 (0.75–7.56)          | 0.82 (0.34–1.95)          |
| ALDH2*1/*2 versus non-flushing                   | 2.90 (1.35–6.22)         | 1.02 (0.41–2.51)          | 0.90 (0.30–2.71)          | 0.97 (0.42–2.21)          |
| MCV ≥ 106 versus <106 fl (≤7 days after the last drink) | 1.15 (0.46–2.86)     | 2.43 (0.78–7.58)          | 1.41 (0.39–5.11)          | 1.56 (0.59–4.16)          |
| Multiple versus solitary intraesophageal SCC at baseline | 3.09 (1.41–6.78) | 2.41 (0.96–6.05) | 3.73 (1.22–11.41) | 3.25 (1.41–7.47) |
| Smoking, per 10+ cigs/day                        | 1.08 (0.85–1.38)         | 1.09 (0.87–1.35)          | 0.86 (0.59–1.24)          | 1.29 (0.98–1.97)          |
|                                                   | 1.22 (1.12–1.32)         | 1.09 (0.87–1.35)          | 0.86 (0.59–1.24)          | 1.29 (0.98–1.97)          |
| **Adjusted for age, alcohol consumption, and all selected variables** |                          |                            |                            |                            |
| ALDH2*1/*2 versus *1/*1                          | 3.22 (1.36–7.64)         | —                         | 12.08 (1.52–95.89)         | —                         |
| Multiple versus solitary intraesophageal SCC at baseline | 2.84 (1.30–6.24) | 2.41 (0.96–6.05) | —                         | 4.27 (1.79–10.16) |
| Smoking, per 10+ cigs/day                        | —                         | —                         | —                         | 1.46 (1.08–1.97)          |

1No. of subjects analyzed for alcohol flushing and mean corpuscular volume (MCV) (e.g. 72 and 55, respectively, for esophagus) was smaller because of missing values. Patients treated by methods other than endoscopic mucosal resection alone at baseline were excluded. Patients who had oropharyngolaryngeal cancer at baseline were excluded. Alcohol flushing was classified on the basis of the results of an alcohol flushing questionnaire; selected by the stepwise procedure with P < 0.10 from all risk factors listed above except alcohol flushing and MCV because of missing values. Age and alcohol consumption were forced into the model. Body mass index (BMI) and alcohol dehydrogenase-1B (ADH1B) genotype were not selected for any cancer site. 175th percentile among all patients. —, not selected; CI, confidence interval; HR, hazard ratio.
lower sensitivity of alcohol flushing as a marker of inactive ALDH2 in alcoholics with less-active ADHIB*1/*1.[21,22] When current/former flushing individuals were assumed to have inactive ALDH2, the sensitivity of current/former flushing for identifying inactive ALDH2 was 52% in the esophageal SCC alcoholics with less-active ADHIB*1/*1. Among the 23 patients with metachronous oropharyngolaryngeal SCC, 9 of the 19 ALDH2*1/*2 heterozygotes had ADHIB*1/*1, and 6 of these 9 reported never having experienced alcohol flushing.

As alcoholic patients often fail to appear for regular follow-up examinations, especially when they relapse into alcohol use, we are unable to report the true incidence of metachronous carcinoma in the entire cohort, however, the reasons for the follow-up examinations included readmission because of a relapse of alcoholism. The background characteristics of the follow-up patients might have affected their risk of metachronous SCC compared to the patients who stopped appearing for follow-up examinations. Our endoscopic follow-up examinations detected metachronous carcinoma in the very early stages, and only 3 of the metachronous SCC patients had symptoms attributable to the SCC lesions prior to the follow-up screening. Thus, it is unlikely that the symptomatic cases biased the results greatly.

Another limitation of our study is that technical improvements in endoscopes and growing understanding of the endoscopic findings of very early SCC in the oropharynx and hypopharynx[35,36] have been achieved during the study period (1993–2007). The Olympus Q240 and Q240Z panendoscopes provided much clearer images than the older models. The results of this study should be confirmed by studies using advanced technology and diagnostic methods.

Treatment of superficial esophageal SCC by EMR has succeeded in improving the outcome of this high-mortality cancer.[27] We have extended the application of EMR and endoscope-guided mucosectomy to superficial SCC of the oropharyngolarynx.[37] The findings in this study warrant intensive follow-up examinations of alcoholics after treatment for esophageal SCC (e.g., every 6 months) by endoscopy combined with esophageal iodine staining and oropharyngolaryngeal inspection. ALDH2*1/*2 and multiple intraesophageal SCC are predictors of metachronous carcinoma in the UADT in this high-risk population.

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