Abstract

The risk of the future development of primary esophageal cancer after endoscopic esophageal mucosal resection of esophageal cancer is not known; hence, there are no established guidelines for follow-up surveillance programs. Simultaneous occurrence of multiple cancers associated with esophageal cancer is common among heavy drinkers who have the inactive form of aldehyde dehydrogenase-2 (ALDH2) as a risk factor. Thirty-four Japanese male alcoholics with intraepithelial or mucosal squamous cell carcinoma in the esophagus were treated by endoscopic esophageal mucosal resection, followed by endoscopy and esophageal iodine staining, to find the additional development of primary esophageal cancer. Primary esophageal squamous cell carcinoma was detected in nine patients (26.5%) at 3-21 months after the first cancer diagnosis. Cancer occurred more frequently in patients with inactive ALDH2 than it did in those with active ALDH2 (42.1% (8 of 19) versus 6.7% (1 of 15), \(P = 0.047\)) and it occurred more frequently in those with multiple esophageal cancers than it did in those without them (60.0% (6 of 10) versus 12.5% (3 of 24), \(P = 0.009\)). Kaplan-Meier estimates of the proportions of patients with additional primary esophageal cancers showed that patients with inactive ALDH2 (\(P = 0.024\)) or multiple esophageal cancers (\(P = 0.007\)) had a significantly increased likelihood of the development of additional cancer. Close follow-up examinations using endoscopy and iodine staining are needed for such high-risk patients.

Introduction

Epidemiological studies have consistently shown that the development of esophageal cancer is strongly related to drinking alcoholic beverages (1). By systematically screening a large population of Japanese male alcoholics, using upper gastrointestinal endoscopy and esophageal iodine staining, we found a high prevalence of superficial esophageal cancer among these subjects (2). Subsequently, we discovered that the inactive form of ALDH2,\(^\text{\textsuperscript{1}}\) encoded by the gene ALDH2\(^*1/2\), is a risk factor for esophageal cancer (3). Approximately 50% of Japanese alcoholics with esophageal cancer have inactive ALDH2, compared with ~10% of control alcoholics (3, 4). Moreover, inactive ALDH2 was associated with simultaneous multiple primary esophageal cancer and concurrent upper aerodigestive tract cancer, both of which occur frequently in heavy drinkers (4, 5).

The frequent occurrence (10-40%) of second malignancies in the head and neck, esophagus, and lungs of patients with primary head and neck cancer is a long-recognized phenomenon (6-9). Both alcohol drinking and tobacco smoking have been reported to be significant predictors of the likelihood of developing second cancer (9, 10), suggesting that these two agents act as carcinogens on the entire epithelium of these areas to produce multiple independent malignant foci. In patients with esophageal cancer, metachronous development of second primary cancers in the head and neck is not uncommon (10-12), but little is known about the risk for other primary cancers in the esophagus per se because of the frequent extirpation of this organ by total esophagectomy.

The majority of cancerous esophageal lesions detected in our screening program were treated by EEMR, according to established criteria (2, 13). In this procedure, the local portions of the mucosa and submucosa containing cancers are removed, and therapeutic results are achieved when esophageal cancers have not invaded the muscularis mucosa. Cancerous involvement of lymph nodes, lymphatics, and vessels is extremely rare in mucosal carcinomas (13, 14). Short-term follow-up inspection of the esophagus after EEMR gave us an opportunity to observe the natural course of very early high-rate development of other esophageal cancer. Seeking determinants of the development of other primary esophageal cancers in alcoholics, we explored the association of additional esophageal cancer with drinking, smoking, ALDH2 genotypes, and histological findings of the first cancer.

\(^{1}\) The abbreviations used are: ALDH2, aldehyde dehydrogenase-2; EEMR, endoscopic esophageal mucosal resection.
Materials and Methods
This study was reviewed and approved by the Ethics Committee of the National Institute on Alcoholism of Japan, and informed consent was obtained from the participating patients.

From January 1993 to March 1997, we systematically screened 1500 Japanese male alcoholics (age ≥40 years) who were consecutively admitted to the National Institute on Alcoholism, Kurihama National Hospital (Kanagawa, Japan), by upper gastrointestinal endoscopy combined with esophageal iodine staining, as described elsewhere (2). Esophageal squamous cell carcinoma was diagnosed in 53 patients by the initial screening and in 4 patients by the follow-up screening, respectively. Thirty-eight patients with intraepithelial or mucosal carcinoma in the esophagus were treated by EEMR without adjuvant therapy. Four of the 38 patients refused follow-up examination. The follow-up plan in the remaining 34 patients was to see them by endoscopy combined with esophageal iodine staining and targeted biopsy at 1 and 4 months after EEMR and every 6 months thereafter. We chose 5 mm in greatest dimension of distinct iodine-unstained lesions as the minimum requirement for biopsy because most carcinomas identified as the iodine-unstained areas were previously reported to be ≥5 mm in greatest dimension (15).

The diagnosis of additional primary carcinomas of the esophagus was based on endoscopic examination using iodine staining, microscopic examination of the resected specimens, and the following criteria for the cancerous lesions: (a) localized lesions (with no continuity with the first cancer sites); (b) lesions' inclusion of areas of intraepithelial carcinoma; and (c) confirmed absence of lesions on the photographic pictures of esophageal iodine staining, which were taken at intervals of at least every 5 cm down along the esophagus at the time esophageal cancer was first diagnosed (retrospective review). When the cancerous lesions were found with continuity with the first cancer sites, they were judged as local recurrences of the first cancer.

Information on the patients' drinking profiles and smoking habits was obtained from the patients and, when available, their partners. The information obtained at the initial screening included the subjects' usual choice of alcoholic beverage, daily alcohol consumption during the preceding year, and the duration (years) of habitual drinking. With regard to smoking, pack-years (number of cigarettes/20 per day × number of years of smoking) was calculated. Information was also obtained about patients' drinking habits after the initial screening. The diagnostic methods of the depth (2) and multiplicity (5) of the first esophageal cancer were described in the previous reports.

The PCR-RFLP method was used for ALDH2 genotyping of lymphocyte DNA samples from these patients (16).

Data were expressed as mean ± SD, and the significance of differences was assessed by the Mann-Whitney U test. Either the Fisher's exact test or the Mantel extension test was used in comparing group frequencies. The percentages of patients with additional primary esophageal cancer were calculated according to the Kaplan-Meier method. The effects of selected variables on the additional development of primary esophageal cancer were assessed with the log-rank test and the Cox proportional hazards model. All analyses were done using the SAS statistical package (Version 6.12; SAS Institute, Cary, NC).

Results
Among 34 patients followed from 6 to 48 months (mean = 22 months), 9 developed primary esophageal squamous cell carcinoma(s) (26.5%; Table 1). A squamous cell carcinoma detected in the esophagus in another patient was judged to be a local recurrence of previously and incompletely resected carcinoma, due to its continuity with the first cancer site. Other carcinomas were found in completely different locations (at distances of >1 cm) from those of the first carcinomas. Multiplicity of the esophageal carcinomas was observed in two patients. All 11 new cancers were detected at 9 months, and the greatest dimension of iodine-unstained areas of cancerous lesions in the esophagus ranged from 5 to 30 mm. The esophageal carcinoma was confined within the epithelium in six patients, to the proper mucosal layer in three, and to the submucosa in two. The intraepithelial or mucosal cancers were detected at 3–21 months. One submucosal carcinoma was detected at 19 months in a patient who had already developed another intraepithelial cancer at 9 months. This submucosal carcinoma existed in the upper third of the esophagus, whereas all other esophageal cancers were located in the middle or lower third of the esophagus. Intraepithelial and mucosal carcinomas were treated by EEMR or laser irradiation, and submucosal carcinomas were treated by surgery (Table 1).

Table 2 compares the drinking and smoking habits, ALDH2 genotypes, and histological findings of the first cancer of the patients, with and without additional primary cancer. There were no differences between the groups in age, duration of follow-up period, drinking habits, smoking habits, or depth of the first cancer. Primary carcinomas occurred more fre-
quently in patients with the *ALDH2*1/2*2* genotype than in those with the *ALDH2*1/2*1* genotype (42.1% versus 6.7%, \( P = 0.047 \)), and they occurred more frequently in those with first multiple intraesophageal cancers than they did in those without them (60.0% versus 12.5%, \( P = 0.009 \)). All of the patients who developed primary carcinoma were *ALDH2*1/2*2* heterozygotes or had multiple cancers at first diagnosis.

Kaplan-Meier estimates of the proportions of patients with additional primary esophageal cancer as a function of time are shown in Figs. 1 and 2. Additional primary esophageal cancers developed significantly more frequently among *ALDH2*1/2*2* heterozygotes and patients with multiple intraesophageal cancers than they did among *ALDH2*1/2*1* homozygotes (\( P = 0.024 \); Fig. 1) and among patients with solitary intraesophageal cancer (\( P = 0.007 \); Fig. 2), respectively, by the log-rank test.

Use of the Cox proportional hazards analysis enabled determination of the relative hazard for the additional esophageal cancer: 7.55 (95% confidence interval; 0.94–60.58, \( P = 0.057 \)) in *ALDH2*1/2*2* heterozygotes, compared with *ALDH2*1/2*1* homozygotes, and 5.52 (95% confidence interval; 1.39–22.25, \( P = 0.016 \)) in patients with multiple intraesophageal cancers, compared with those who had solitary intraesophageal carcinoma.

**Discussion**

We previously reported a high prevalence of simultaneous multiple intraesophageal cancers among alcoholics with heterozygous *ALDH2*1/2*2* (5). The majority of the early esophageal cancers detected were treated by EEMR (2). The time course of development of further primary esophageal cancers after EEMR is not known; hence, there is no guideline for longitudinal follow-up examinations. In this follow-up study, we observed that primary esophageal cancers developed frequently during short intervals and that they were strongly associated with the inactive form of *ALDH2* and the multiplicity of the first esophageal cancers.

Inactive *ALDH2* is slow to oxidize the ethanol metabolite, acetaldehyde (17), a recognized animal carcinogen (18), leading to excessive accumulation of acetaldehyde after drinking (19). In the population studied, the inactive *ALDH2* was predictive of the development of new cancers, suggesting that systemic acetaldehydeemia plays a crucial role in multicentric or field cancerization throughout the entire esophageal surface.

Additional primary cancers were detected within the relatively short time of 2 years after the first cancer diagnosis, even in alcoholics who had abstained from drinking. Rather than being second primary cancers, these cancers may have existed as indistinct lesions at the initial screening, subsequently becoming distinct lesions that are large enough to be identifiable. Although the photographic records of the esophageal iodine staining did not demonstrate the presence of those primary cancers, even upon retrospective review, in the initial examinations of most alcoholics with esophageal cancer, we did observe numerous minute areas that did not take up iodine. The possibility that some of these glycogen-poor areas were dysplastic or cancerous foci cannot be ruled out.

Seven patients in our intensive follow-up program were found to have esophageal carcinoma lesions that were confined to the epithelium or proper mucosal layer and treated by second EEMR. However, at 19 months of follow-up, two additional patients were diagnosed as having esophageal carcinomas with submucosal involvement. Both had failed to show up for their regular 6-month checkups. These results legitimize intensive follow-up examinations by endoscopic observation combined with esophageal iodine staining at least every 6 months for alcoholics, especially those who are *ALDH2*1/2*2* heterozygotes or who have multiple cancers. Final rinsing of the esophageal mucosa with thiosulfate solution lessens the irritation caused by iodine; this rinse renders the frequent iodine staining acceptable to and well tolerated by the patients (2).

Although these patients are at high risk for further primary cancers, the advantage of EEMR over definitive therapy (esophagectomy) is apparent, provided the patients receive intensive follow-up examinations for further early carcinomas. EEMR is a safe and effective procedure for early esophageal
first cancer increase the risk for rapid development of other primary cancer in Japanese alcoholics. Close follow-up examination every 6 months, using endoscopy and iodine staining, is needed for these high-risk patients.

References

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