

REVIEW

Alcohol and Aldehyde Dehydrogenase Polymorphisms and a New Strategy for Prevention and Screening for Cancer in the Upper Aerodigestive Tract in East Asians

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The ethanol in alcoholic beverages and the acetaldehyde associated with alcohol consumption are Group 1 human carcinogens (WHO, International Agency for Research on Cancer). The combination of alcohol consumption, tobacco smoking, the inactive heterozygous aldehyde dehydrogenase-2 genotype (*ALDH2*1/*2*) and the less-active homozygous alcohol dehydrogenase-1B genotype (*ADH1B*1/*1*) increases the risk of squamous cell carcinoma (SCC) in the upper aerodigestive tract (UADT) in a multiplicative fashion in East Asians. In addition to being exposed to locally high levels of ethanol, the UADT is exposed to a very high concentration of acetaldehyde from a variety of sources, including that as an ingredient of alcoholic beverages *per se* and that found in tobacco smoke; acetaldehyde is also produced by salivary microorganisms and mucosal enzymes and is present as blood acetaldehyde. The inefficient degradation of acetaldehyde by weakly expressed ALDH2 in the UADT may be critical to the local accumulation of acetaldehyde, especially in *ALDH2*1/*2* carriers. *ADH1B*1/*1* carriers tend to experience less intense alcohol flushing and are highly susceptible to heavy drinking and alcoholism. Heavy drinking by persons with the less-active *ADH1B*1/*1* leads to longer exposure of the UADT to salivary ethanol and acetaldehyde. The *ALDH2*1/*2* genotype is a very strong predictor of synchronous and metachronous multiple SCCs in the UADT. High red cell mean corpuscular volume (MCV), esophageal dysplasia, and melanosis in the UADT, all of which are frequently found in *ALDH2*1/*2* drinkers, are useful for identifying high-risk individuals. We invented a simple flushing questionnaire that enables prediction of the ALDH2 phenotype. New health appraisal models that include ALDH2 genotype, the simple flushing questionnaire, or MCV are powerful tools for devising a new strategy for prevention and screening for UADT cancer in East Asians. (Keio J Med 59 (4) : 115–130, December 2010)

Keywords: acetaldehyde, alcohol dehydrogenase, aldehyde dehydrogenase, esophageal cancer, head and neck cancer

Introduction

Alcohol consumption and tobacco smoking are two major risk factors for squamous cell carcinoma (SCC) of the upper aerodigestive tract (UADT; the oral cavity, pharynx, larynx, and esophagus) in developed countries,

and these factors synergistically increase the cancer risk. A large Japanese case-control study demonstrated that a combination of drinking (≥ 33 g ethanol/day) and heavy smoking (≥ 30 pack-years) posed the highest risk of esophageal and hypopharyngeal cancer [odds ratio (OR; 95% confidence interval) = 29.9 (10.9–81.9)] in compar-

ison with the combination of never drinking and never smoking, whereas the OR was 8.2 (2.4–27.7) for the combination of drinking (≥ 33 g ethanol/day) and never smoking and 3.9 (1.3–11.8) for the combination of heavy smoking and never drinking.¹ Adequate intake of fruits and vegetables is associated with a reduced risk of SCC in the UADT. A recent Japanese prospective cohort study demonstrated that an increase in total fruit and vegetable intake by 100 g/day was associated with an 11% (1%–21%) decrease in the incidence of esophageal SCC,² and the protective effect of fruits and vegetables was greater in heavy drinkers and smokers. Low body mass index (BMI) is another risk factor for SCC in the UADT.³ A case-control study⁴ and a prospective study⁵ in Japanese alcoholics showed that alcoholics with a BMI < 19.0 (lowest quartile) had a substantially higher risk of SCC in the UADT than those with a BMI ≥ 23.2 –23.7 [highest quartile; OR = 4.6 (1.8–11.7) for esophageal SCC and hazard ratio (HR; 95% confidence interval) = 3.6 (1.2–11.1) for SCC in the UADT]. Many Japanese alcoholic patients are also heavy smokers, and their poor nutritional status and low BMI are largely attributable to poor dietary habits, including a low intake of green and yellow vegetables, and smoking.⁶

We introduced an endoscopic screening program at Kurihama Alcoholism Center in 1993,⁷ and by 2008, initial screening of 5210 Japanese alcoholic men by endoscopy combined with oropharyngolaryngeal inspection and esophageal iodine staining had detected esophageal SCC in 206 (4.0%) and oropharyngolaryngeal SCC in 55 (1.1%). Recent technical improvements in endoscopes and a growing understanding of the endoscopic findings of early SCC in the esophagus^{7,8} and pharynx⁹ have enabled very early detection of SCC in the UADT. Treatment of early esophageal SCC by endoscopic mucosectomy has become widespread in Japan and has succeeded in improving the outcome of this high-mortality cancer^{10,11}; early pharyngeal SCC is also now being treated by endoscope-guided mucosectomy¹² with excellent outcomes.¹³ It has thus become even more important to develop preventive strategies and screening programs based on risk factors.

Genetic Polymorphism of ALDH2 and Alcohol Metabolism

A mutant allele encoding an inactive subunit of aldehyde dehydrogenase-2 (ALDH2; rs671) was carried by the Han Chinese as they spread throughout East Asia.¹⁴ Its highest frequency has been found in Southeast China, and inactive ALDH2 is observed in most areas of China, Japan, Korea, Mongolia, and Indochina, but is not found in most other populations. About 40% of Japanese have the inactive *ALDH2**2 allele (e.g., 7% are homozygous and 35% are heterozygous),¹⁵ which acts in a dominant manner. After drinking 0.1 g ethanol/kg body weight,

homozygotes for inactive ALDH2 and heterozygotes for inactive ALDH2 had 18 times higher and 5 times higher peak blood acetaldehyde concentrations, respectively, than active *ALDH2**1/*1 homozygotes who had consumed 0.8 g ethanol/kg body weight.¹⁶ An alcohol challenge test showed a 7% slower ethanol elimination rate among Japanese with the *ALDH2**1/*2 genotype than with the *ALDH2**1/*1 genotype, suggesting product inhibition of ethanol oxidation by high blood acetaldehyde levels in *ALDH2**1/*2 heterozygotes.¹⁷ After drinking a relatively small amount of alcohol, people with inactive ALDH2 tend to experience a flushing response, including facial flushing, palpitations, nausea, and drowsiness,¹⁸ and they experience a hangover the next morning.¹⁹ Having inactive ALDH2 generally prevents East Asians from drinking heavily. Homozygotes for inactive ALDH2 are usually non-drinkers or occasional drinkers because of their very intense flushing responses, but 26% of heavy drinkers²⁰ and 13% of alcoholics¹⁵ in Japan have been found to be heterozygous for inactive ALDH2 in Japan.

ALDH2 and SCC in the UADT Esophageal SCC in Japan and Taiwan

In 1996, we first reported that the heterozygous inactive ALDH2 genotype is a strong risk factor for esophageal cancer in everyday drinkers and alcoholics.²¹ Since then, Japanese and Taiwanese case-control studies have shown that approximately 65%–76% of esophageal cancer patients^{20–28} and 53%–63% of alcoholics with esophageal cancer^{21,29–31} had the *ALDH2**1/*2 genotype, and the studies have consistently demonstrated strong associations.³³ In a study in which alcoholics with no evidence of cancer based on endoscopic screening served as controls, the OR for detection of esophageal SCC by screening heterozygote alcoholics with inactive ALDH2 was 13.5-fold (8.1–22.6) the OR of alcoholics with active ALDH2.³¹ We conducted a multicenter case-control study of 234 esophageal SCC cases and 634 controls²⁰ and found that the OR of moderate drinkers (198–365 g ethanol/week) with the *ALDH2**1/*2 genotype was 55.8 (15.4–202.5) when never/rare drinkers (< 22 g ethanol/week) were used as the reference group, and that far exceeded the OR of 10.4 (2.9–37.8) of heavy drinkers (≥ 396 g ethanol/week) with the *ALDH2**1/*1 genotype (**Fig. 1A**). Estimation of population attributable risk (PAR) revealed that alcohol-drinking *ALDH2**1/*2 heterozygotes accounted for 69% of the cancer cases. The PAR was 31% for preference for drinking strong alcoholic beverages straight, 54% for smoking, 26% for low intake of green-yellow vegetables, and 38% for low intake of fruits. If ALDH2 heterozygotes who consume 198 g ethanol/week or more consumed less than 198 g ethanol/week instead, 53% of esophageal cancers might be prevented in this population.³⁴ The ORs for the devel-

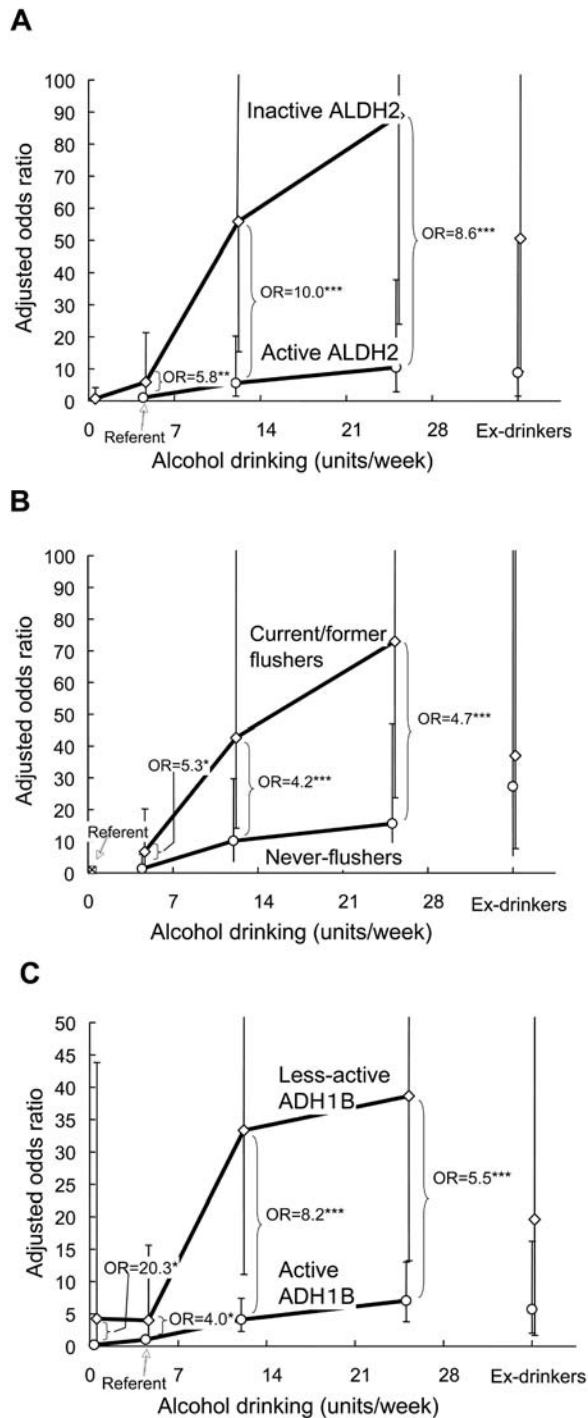


Fig. 1 Alcohol drinking by Japanese men and risk of esophageal squamous cell carcinoma according to (A) ALDH2 genotype,²⁰ (B) alcohol flushing,¹⁰⁶ and (C) ADH1B genotype.²⁰ The subjects were classified as never/rare drinkers, current drinkers who consumed 1 to 8.9 units/week (light drinkers; 1 unit = 22 g ethanol), 9 to 17.9 units/week (moderate drinkers), or 18+ units/week (heavy drinkers), or ex-drinkers. Odds ratios were adjusted for age, frequency of drinking strong alcoholic beverages straight, pack-years of smoking, frequency of intake of green and yellow vegetables, and frequency of fruit intake. The vertical lines indicate the 95% confidence interval. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

opment of esophageal cancer of Taiwanese drinkers with inactive heterozygous ALDH2 are also markedly high.^{26,27} Persons who have the inactive *ALDH2**1/*2 genotype and are in the habit of drinking more than 30 g ethanol/day have a 103-fold (38–275) greater odds of developing esophageal cancer than non-drinkers with the active *ALDH2**1/*1 genotype, and a PAR of 58% for alcohol-drinking *ALDH2**1/*2 heterozygotes was found.²⁷ A meta-analysis showed that ALDH2-related susceptibility to esophageal cancer includes light-to-moderate drinkers as well as heavy drinkers.³⁵ The magnitude of the *ALDH2**1/*2-associated risk was 7.07 (3.67–13.60) times in heavy drinkers and 2.49 (1.29–4.79) times in light-to-moderate drinkers.

A Japanese case-control study of women showed a markedly higher risk [OR = 59.1 (4.65–750)] of esophageal SCC in heavy drinkers (≥ 396 g ethanol/week) with the *ALDH2**1/*2 genotype than in never/rare drinkers with the *ALDH2**1/*1 genotype; this study also showed a somewhat lower risk in women than in men overall, except among heavy drinkers with the *ALDH2**1/*2 genotype.³⁶ The large recent increase in alcohol consumption among women in Japan may have been too recent for the full effects to have materialized. The reported number of years of alcohol consumption among drinkers was substantially fewer for women than for men, and the women were more health-conscious than men in regard to smoking and dietary habits.

The two largest case-control studies, one in Taiwan³⁷ and the other in Japan,²⁸ showed that the *ALDH2**1/*2 genotype increased the risk of esophageal SCC more in the younger population, suggesting that high acetaldehyde exposure accelerates the development of esophageal SCC at a young age.

Esophageal SCC in Mainland China

In high-risk areas for esophageal cancer in mainland China, there is pronounced heritability of esophageal cancer risk, and alcohol drinking plays a less important role in esophageal carcinogenesis than in Japan and Taiwan. In such a high-risk area, case-control studies have shown modest to moderate positive associations [ORs = 1.67 (1.02–2.72) to 3.12 (1.86–6.58)]^{38–41} or no associations⁴² between inactive ALDH2 and esophageal cancer risk. The *ALDH2**1/*2-associated risk in Chinese studies was stronger where the impact of alcohol consumption on esophageal carcinogenesis was stronger, and when only male populations were evaluated. Over the past 40 years, per-capita alcohol consumption has increased by 9 times in China, whereas it has doubled in Japan. Consumption has remained stable in recent years in Japan, but will probably increase further in China.⁴³ Chinese consumption is still comparable to Japanese consumption in the 1970s, when the number of heavy drinkers with inactive heterozygous ALDH2 started to

increase dramatically.⁴⁴ Alcohol-related esophageal cancer in mainland China will be a greater problem in the future.

Head and Neck Cancer

A meta-analysis of six Japanese case-control studies showed increased *ALDH2**1/*2-related susceptibility to head and neck cancer in moderate drinkers as well as in heavy drinkers compared to *ALDH2**1/*1 genotype,⁴⁵ and the magnitude of the *ALDH2**1/*2 effect on head and neck cancer was greater in heavy drinkers [OR = 3.57 (1.41–9.05)] than in moderate drinkers [OR = 1.68 (1.27–2.22)]. Japanese studies of the *ALDH2**1/*2-associated risk for head and neck cancer have reported different patterns of association according to anatomical site and drinking habit. One case-control study of oral cancer in which alcohol consumption was not a risk factor showed that *ALDH2* genotype had no effect,⁴⁶ but another case-control study of oral cancer in which alcohol consumption was a risk factor reported a relatively weak but significantly increased risk [OR = 2.9 (1.1–7.8)] associated with *ALDH2**1/*2.⁴⁷ A case-control study of oral and pharyngeal SCC showed that *ALDH2**1/*2 was a strong risk factor for SCC in the hypopharynx [OR = 10.1 (3.8–26.8)] among men who were moderate-to-heavy drinkers, but the OR of 1.80 (0.83–3.89) for SCC of the oral cavity and oropharynx did not reach the level of significance.⁴⁸ We conducted a nested case-control study based on the results of the initial endoscopic screening of 3016 Japanese alcoholic men.⁴⁹ In that study 55 cases of SCC of the oropharyngolarynx were detected, and 275 cancer-free controls matched for age and initial examination time were randomly selected to provide a case:control ratio of 1:5. The OR of inactive *ALDH2* heterozygotes versus active *ALDH2* homozygotes for SCC in the oropharyngolarynx as a whole was 4.70 (2.60–8.51), and the OR of inactive *ALDH2* heterozygotes versus active *ALDH2* homozygotes for SCC in the oropharynx/hypopharynx/epilarynx was 6.66 (3.27–13.6). The OR of 1.55 (0.40–5.95) for SCC in the tongue/gingiva/vocal cord, however, did not reach the level of significance. A prospective study of cancer-free Japanese alcoholic men showed similarly high HRs of 13.0 (5.2–32.1) and 11.7 (4.7–29.5) for SCC of the esophagus and oropharyngolarynx in inactive *ALDH2* heterozygotes, respectively, but half of the oropharyngolaryngeal SCCs were hypopharyngeal.⁵ Inactive heterozygous *ALDH2* and initial multiplicity of intra-esophageal SCCs increased the risk of metachronous hypopharyngeal/epilaryngeal SCC in Japanese alcoholic men who had been treated for esophageal SCC [HR = 12.08 (1.52–95.89) and 3.73 (1.22–11.41), respectively], but the positive associations with oral cavity/oropharyngeal SCC did not reach the level of significance [HR = 2.53 (0.82–7.86) and 2.41 (0.96–6.05),

respectively].⁵⁰ The impact of the carcinogenesis-inducing effect of acetaldehyde may differ according to anatomical site.

Field Cancerization

The prevalence of multiple-organ cancer among Japanese esophageal cancer patients in the National Cancer Center has increased at an alarming rate, from 6% in 1969–80 to 22% in 1981–91 and to 39% in 1992–96.⁵¹ The most frequent sites of multiple cancers were the head, neck and stomach. The SEER Program of the U.S. National Cancer Institute has reported synchronous and metachronous multiple cancers in only 2% and 3%, respectively, of esophageal cancer patients between 1973 and 2003.⁵² One reason for the increase in Japan is the improvement in survival rates, which increases the chance of developing other primary cancers. Another reason is the widespread use of esophageal iodine staining to screen head and neck cancer patients for esophageal cancer; this has yielded a very high esophageal cancer detection rate (e.g., 11.8%).⁵³ Yet another reason for the increase in multiple esophageal cancers in Japan is the dramatic increase in the proportion of inactive *ALDH2* heterozygotes among Japanese alcoholics in the same period, from 3% in 1979 to 8% in 1986 and 13% in 1992.⁴⁴ The proportion of inactive *ALDH2* heterozygotes among Han Chinese alcoholics in Taiwan also increased during the 1990s, from 10% to 18%.⁵⁴ The inhibitory impact of inactive heterozygous *ALDH2* on heavy drinking is influenced by sociocultural factors, such as greater peer pressure and greater social acceptance of drinking in Japanese male culture.

Japanese case-control studies and endoscopic follow-up studies have consistently demonstrated that *ALDH2**1/*2 is a strong risk factor for multiple cancerization in the UADT.^{29,31,50,55–59} Alcoholics with the *ALDH2**1/*2 genotype and those with synchronous multiple esophageal SCCs at baseline had a markedly increased likelihood of developing metachronous SCC in the UADT after treatment for esophageal SCC.⁵⁰ Acetaldehyde plays a critical role in multicentric field cancerization throughout the UADT.

The frequency of synchronous and metachronous gastric cancer among esophageal SCC patients is also high in the Japanese population,^{51,60} suggesting the presence of common background factors underlying the gastric and esophageal cancers. We conducted a case-control study based on the results of initial endoscopic screening of 3497 Japanese alcoholic men in which gastric adenocarcinoma was detected at a high rate of 1.4%.⁶¹ In the gastric cancer cases compared with the controls, there was a significantly higher age-adjusted prevalence of patients positive for *Helicobacter pylori* (78% vs. 57%, *P* = 0.022), of severe chronic atrophic gastritis (CAG) assessed by the serum pepsinogen test (49% vs. 15%, *P* <

0.001), of *ALDH2*1/*2* (36% vs. 14%, $P < 0.001$), of mean corpuscular volume (MCV) ≥ 106 fl (38% vs. 20%, $P = 0.008$), and of synchronous SCC in the UADT (18% vs. 5%, $P = 0.004$). Even among the gastric-cancer-free controls, the prevalence of severe CAG was higher than generally reported in Japan, and combinations of CAG and *ALDH2*1/*2* entailed a higher risk of gastric cancer [OR = 4.0 (1.1–14), 17.6 (5.3–58), 9.7 (2.4–39), 17.1 (3.9–76), and 39.2 (6.4–239) for non-severe CAG alone, severe CAG alone, *ALDH2*1/*2* alone, non-severe CAG plus *ALDH2*1/*2*, and severe CAG plus *ALDH2*1/*2*, respectively].

The risk of metachronous gastric cancer in Japanese men after surgery for esophageal cancer has been reported to be twice that of the general Japanese male population.⁶⁰ The risk of metachronous gastric cancer is especially high in Japanese alcoholic men with esophageal SCC: the estimated cumulative rate for metachronous gastric cancer within 5 years was 15% in an alcoholic study,⁶² as opposed to the 10% within 10 years reported in a Japanese non-alcoholic study.⁶⁰ CAG assessed by the serum pepsinogen test and *H. pylori* status were compared in 90 Japanese alcoholic men with esophageal SCC and 180 age-matched Japanese gastric- and esophageal-cancer-free alcoholic men.⁶² The results showed markedly accelerated progression of *H. pylori*-related severe CAG in those with esophageal SCC, indicating the existence of common mechanisms by which both esophageal SCC and severe CAG develop. Endoscopic follow-up in Japanese alcoholic men with esophageal SCC revealed an age-adjusted HR of 7.87 (1.43–43.46) in patients with severe CAG in comparison with those without CAG. Accelerated development of severe CAG partially explained the very high frequency of development of metachronous gastric cancer in this population.

Esophageal Dysplasia

Esophageal dysplasia is rarely detected by endoscopy in the absence of esophageal iodine staining. We have collected mucosal biopsy specimens from distinctly iodine-unstained lesions (DIULs) with a greatest dimension of 5 mm or more, but because we often observed multiple DIULs in alcoholics, especially in those with *ALDH2*1/*2*, we were puzzled as to how to prioritize lesions for biopsy. We noticed that the DIULs changed color, and that most of the cancerous lesions became partially or completely tinged light pink about 2 minutes after staining. We refer to this endoscopic finding as the “pink color sign (PC sign).”⁶³ A comparison of 112 dysplasia lesions and 138 very early cancers revealed that the PC sign was positive in 90% of the cancers but in only 3% of the dysplasia lesions. Another study demonstrated 92% sensitivity and 94% specificity of the PC sign as a means of differentiating high-grade intra-epithelial neoplasia or SCC from other non-cancerous le-

sions when targeted biopsy of 121 DIULs ≥ 5 mm was performed.⁶⁴ The PC sign is a useful endoscopic finding for identifying high-risk cancerous lesions during screening of high-risk drinkers.

In a study in which five deep serial sections were obtained from each biopsy specimen of DIULs ≥ 5 mm detected in alcoholics and stained with hematoxylin and eosin, an expert pathologist in the field of esophageal neoplasia diagnosed 96% of the non-cancerous DIULs as esophageal dysplasia.⁶⁵ The presence of multiple esophageal iodine-unstained lesions and the presence of large esophageal DIULs ≥ 5 mm were correlated with inactive heterozygous *ALDH2*^{58,66–68} and with increased risk of multiple SCCs in the UADT.^{5,58,66,67,69,70}

The 6 year cumulative rates of detection of metachronous SCC in the esophagus and oropharyngolarynx were 56% and 35%, respectively, in Japanese alcoholics after endoscopic mucosectomy of esophageal SCC, as opposed to 31% and 20%, respectively, in those with esophageal dysplasia ≥ 5 mm, and 4% and 4%, respectively, in those without DIULs ≥ 5 mm.⁷¹ Esophageal dysplasia ≥ 5 mm is associated with a very high risk of SCC in the UADT. The presence of multiple esophageal iodine-unstained lesions is a strong predictor of the development of metachronous SCC in the esophagus⁶⁹ and head and neck⁷⁰ in Japanese patients after endoscopic mucosectomy for esophageal SCC.

Melanosis in the UADT

Melanosis of the palate, pharynx, and esophagus is characterized by flat, greenish-black pigmented areas, and it is frequently (11%, 10%, and 7%, respectively) detected during endoscopic screening of Japanese alcoholic men.^{65,68} We have shown that the presence of melanosis indicates a high risk of neoplasia in the UADT. Esophageal dysplasia and SCC in the UADT in alcoholic men were frequently (25% and 49%, respectively) accompanied by melanosis in the UADT. Inactive *ALDH2*, advanced age, and heavy smoking are strongly associated with the presence of melanosis. Some of the causes of melanosis and UADT neoplasia are the same, and they include heavy drinking, inactive *ALDH2*, acetaldehyde exposure, heavy smoking, and advanced age. A high detection rate (19%) of esophageal melanosis by endoscopy has been reported in Japanese esophageal SCC patients at a university hospital.⁷² The above findings are consistent with the results of an earlier pathological study that found a high frequency and high density of melanocytes in surgical specimens obtained from Japanese esophageal cancer patients.⁷³ The detection of melanosis in the UADT may encourage endoscopists to use esophageal iodine staining and to examine the oropharyngolaryngeal sites carefully.

Carcinogenicity of Acetaldehyde

Acetaldehyde is a mutagen, genotoxin, and DNA-damaging agent,⁷⁴ and sufficient evidence of the carcinogenicity of acetaldehyde has been obtained in experimental animals.⁷⁵ Acetaldehyde inhalation has been shown to result in the development of tumors in the respiratory tract, i.e., adenocarcinomas and SCCs of the nasal mucosa in rats⁷⁶ and laryngeal carcinomas in hamsters⁷⁷; in addition, acetaldehyde promotes carcinogenesis by benzo(a)pyrene in hamsters.⁷⁷ We have demonstrated high blood levels of mutagenic acetaldehyde-DNA adducts in alcoholics with heterozygous inactive ALDH2.⁷⁸ The formation of DNA adducts may explain many of the genotoxic effects of acetaldehyde. Other human evidence includes a high frequency of sister chromatid exchanges⁷⁹ and micronuclei⁸⁰ and slower electrophoretic DNA migration⁸¹ by leukocytes from habitual drinkers with inactive heterozygous ALDH2. The International Agency for Research on Cancer (IARC) of the WHO has noted that the substantial mechanistic evidence obtained in ALDH2-deficient humans indicates a causal role of acetaldehyde in esophageal cancer.⁸² It classified the ethanol in alcoholic beverages as a Group 1 carcinogen in 2007⁸² and the acetaldehyde associated with alcohol consumption as a Group 1 carcinogen in 2009.⁸³ Classification as a Group 1 carcinogen means there is sufficient evidence of carcinogenicity in humans.

Salivary Acetaldehyde

Alcohol challenge tests that monitor blood and salivary acetaldehyde concentrations after a moderate dose of alcohol^{84,85} have shown much higher salivary acetaldehyde concentrations than blood acetaldehyde concentrations in both inactive ALDH2 heterozygotes (e.g., 37–76 μM vs. 12–25 μM)⁸⁵ and active ALDH2 homozygotes (e.g., 24–53 μM vs. 2–5 μM). Most experimental studies on mammalian or human cell cultures have shown induction of mutations, sister chromatid exchanges, and chromosomal aberrations after exposure to acetaldehyde concentrations ranging from 40 to 1000 μM in a highly dose-dependent manner.⁸⁶ The acetaldehyde levels measured in the saliva of healthy persons may be sufficient to cause mutagenic damages in the UADT. Normal oral bacteria and yeasts produce acetaldehyde from ethanol, and they make a large contribution to the high acetaldehyde level in saliva. The *in vitro* acetaldehyde producing ability of saliva is abolished by sterile filtration or centrifugation,⁸⁶ and it has been found to be correlated with both salivary microbial counts and salivary acetaldehyde levels after drinking.^{87,88} The salivary acetaldehyde levels after drinking were reduced after using an antiseptic mouthwash⁸⁶; 4-methylpyrazole, a weak inhibitor of microbial alcohol dehydrogenase (ADH) but a strong inhibitor of mucosal and hepatic

ADH, decreased the salivary acetaldehyde concentration of *ALDH2*1/*2* subjects but not of *ALDH2*1/*1* subjects.⁸⁹ Heavy drinking,^{87,88} smoking,⁸⁷ and poor oral hygiene,⁹⁰ all of which are common in alcoholics, are associated with increased salivary acetaldehyde-producing capacity, probably as a result of modification of the oral microflora. Both the oral microbial counts and *in vitro* salivary acetaldehyde-producing capacity of Japanese alcoholics decreased after 3 weeks of abstinence, and the decreases were mutually correlated.⁸⁸ Many factors in addition to abstinence, including tooth-brushing behavior and diet, may have changed during the 3-week abstinence period. Overgrowth of oral microorganisms resulting in excessive production of salivary acetaldehyde is another possible explanation for the very high rate of UADT cancer in alcoholics.

Acetaldehyde in Alcoholic Beverages

Alcoholic beverages themselves contain high levels of acetaldehyde.⁹¹ The French apple brandy Calvados, the Japanese distilled liquor *shochu*, and other spirits in undiluted form have an acetaldehyde concentration of 1000 μM .^{85,91} In a randomized cross-over design study in which 19 healthy Japanese volunteers ingested 0.6 g ethanol/kg body weight in the form of 13%-ethanol Calvados, 13%-ethanol *shochu*, 13%-ethanol red wine, and 5%-ethanol beer under fasting conditions at 3-week intervals,⁸⁵ the acetaldehyde concentration of the beverages consumed was 600 μM , 600 μM , 250 μM , and 140 μM , respectively. The results showed that the salivary acetaldehyde concentrations immediately after drinking the high-acetaldehyde beverages were higher than immediately after drinking the low-acetaldehyde beverages. Overall trends suggest that consumption of all types of alcoholic beverages increases the risk for SCC in the UADT, but Japanese studies have shown stronger associations between SCC in the UADT and a preference for drinking concentrated alcoholic beverages, such as whiskey and *shochu*, straight.^{20,48,92} The high level of direct exposure of the UADT to acetaldehyde as well as to ethanol, at least in part, explains the increased susceptibility to cancer of the UADT as a result of the preference for drinking high ethanol/acetaldehyde beverages straight.

Acetaldehyde in Tobacco Smoke

The results of a large genome-wide association study involving 1070 Japanese esophageal SCC patients and 2836 controls demonstrated that four risk factors [i.e., inactive heterozygous ALDH2, less-active ADH1B (see below), drinking, and smoking] synergistically increase the risk of esophageal cancer.²⁸ The effects of combination of the high-risk genotypes were more prominent in smokers and in heavier drinkers. Interestingly, the increase in risk associated with having the *ALDH2*1/*2*

genotype was greater in smokers than in non-smokers, but the increase in risk associated with less-active ADH1B was similar in smokers and non-smokers. Although alcohol consumption in each drinking category may have been greater in the smokers than in the non-smokers, the acetaldehyde in tobacco smoke is another possible explanation for these findings. As one of the major chemical constituents of tobacco smoke, acetaldehyde dissolves in saliva during active smoking and reaches concentrations as high as 400 μM .⁹³ Inefficient degradation of the acetaldehyde in inactive ALDH2 heterozygotes may lead to accumulation of very high levels of acetaldehyde in the mucosa of the UADT after high exposure to acetaldehyde during active smoking.

Acetaldehyde Metabolism in the Mucosa of the UADT

High-Km ADH7 (class IV ADH) is strongly expressed in the UADT and it actively catalyzes conversion of ethanol to acetaldehyde upon exposure to a locally high dose of ethanol.^{94,95} ADH7 activity is higher in esophageal cancer cells than in normal esophageal tissue, suggesting that increased ADH7 activity may be a factor intensifying carcinogenesis through increased mucosal acetaldehyde production.⁹⁶ Chronic alcohol consumption leads to induction of cytochrome P4502E1, which metabolizes ethanol to acetaldehyde,⁹⁷ and induction of P4502E1 has been demonstrated in the oropharyngeal mucosa of alcoholics with oropharyngeal cancer.⁹⁸ The epithelium of the UADT of alcoholics is exposed to a very high concentration of acetaldehyde from a variety of sources. ALDH activity is disproportionately lower than ADH activity in the UADT.^{94,95} The results of immunohistochemical staining of the esophageal mucosa with ALDH2-antibody in Japanese esophageal cancer patients have suggested that both inactive and active forms of ALDH2 are induced in normal esophageal epithelium by heavy drinking,⁹⁹ and this enzyme induction may widen the difference in mucosal acetaldehyde elimination between *ALDH2*1/*1* and *ALDH2*1/*2* alcoholics. During exposure to very high levels of acetaldehyde, the inefficient degradation of acetaldehyde by tissue ALDH2 in the UADT may be more critical to the difference in local accumulation of acetaldehyde between individuals with *ALDH2*1/*1* and *ALDH2*1/*2*.

The Simple Flushing Questionnaire

ALDH2-associated cancer susceptibility emphasizes the importance of developing screening tests for inactive ALDH2 based on alcohol flushing.³⁴ The results regarding associations between alcohol flushing and ALDH2 genotype have been found to differ markedly according to how the question about alcohol flushing is posed. Without defining the alcohol dose, answers to the ques-

tion, “Do you currently experience facial flushing after drinking alcohol?” are unreliable as a means of predicting the presence of inactive ALDH2. Half of active ALDH2 carriers have been found to be always flushers or occasional flushers when asked this question, probably because they experienced alcohol flushing when they drank a substantial amount of alcohol.¹⁰⁰ The results of a Japanese cohort study in which this question was asked showed that 49% of flushers had active ALDH2 and that the flushing-associated risk of esophageal cancer was modest, but that the hazard risk was greatest for flushers who were also both heavy drinkers and heavy smokers.¹⁰¹

There have been several important advances in the methods used to predict the presence of inactive ALDH2 based on replies to questionnaires on alcohol flushing responses. Takeshita and Morimoto developed an alcohol sensitivity screening test based on flushing responses that had an 89% sensitivity and 90% specificity when applied to 424 Japanese male workers.¹⁰² The ethanol patch test, a cutaneous test for the flushing response, is used in Japan in health education for youths, especially those who have never consumed alcohol. The first study reported a high sensitivity (93%) and specificity (94%) for identifying inactive ALDH2,¹⁰³ but subsequent studies failed to confirm such high reliability levels.^{102,104,105} The sensitivity of 72% and specificity of 71% of the ethanol patch test among men age 50 or older, many of whom had a long history of drinking, were unsatisfactory,¹⁰⁵ suggesting that aging and acquired tolerance to acetaldehydemia influence the test results.

When the current flushing question, “Do you have a tendency to flush in the face immediately after drinking a glass of beer?” (a glass means about 180 mL, the most common Japanese beer glass size), was used to detect inactive ALDH2, its specificity for detecting active ALDH2 was very high, but its sensitivity for detecting inactive ALDH2 was only 74% in cancer-free men, 57% in men with esophageal cancer, and 8% in alcoholic men with esophageal cancer.^{106,107} Alcohol flushing diminishes in intensity as a result of the development of tolerance to acetaldehydemia in higher-risk persons with a long or heavy drinking history.

We devised a flushing questionnaire to resolve the above problems (Fig. 2).¹⁰⁶ The simple flushing questionnaire consists of two questions: (A) Do you have a tendency to flush in the face immediately after drinking a glass (180 mL) of beer? (B) Did you have a tendency to flush in the face immediately after drinking a glass of beer during the first to second year after you started drinking? We classified the results as current flushing, former flushing, or never flushing. When current flushers and former flushers were assumed to have inactive ALDH2, the simple flushing questionnaire yielded 90% sensitivity and 88% specificity among 610 Japanese men aged 40 years or older¹⁰⁶ and 88% sensitivity and 92%

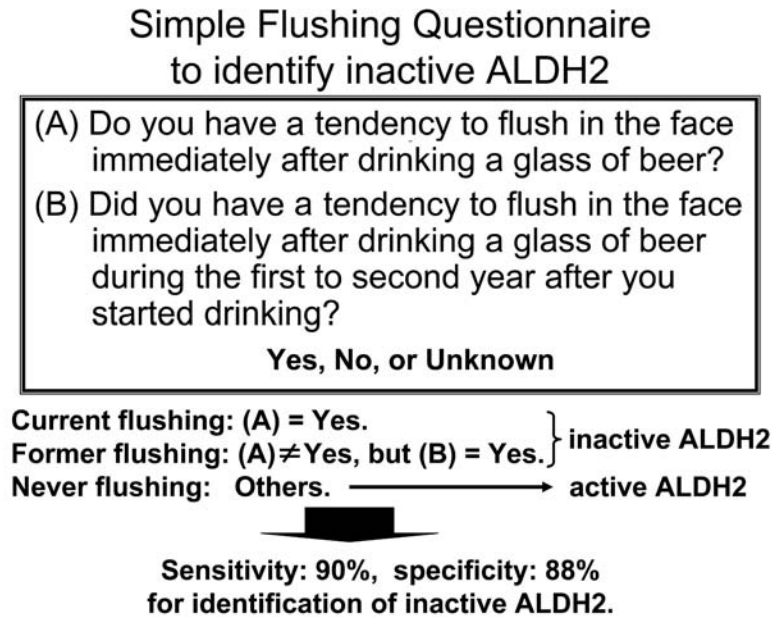


Fig. 2 The simple flushing questionnaire to identify inactive ALDH2. Sensitivity and specificity are both approximately 90% in Japanese subjects 40 years of age and over regardless of gender.^{36,106}

specificity among 381 Japanese women aged 40 years or older.³⁶ The individuals' risks of UADT cancer estimated on the basis of the replies to the flushing questionnaire were slightly lower than, but basically comparable to, those estimated on the basis of ALDH2 genotyping (**Fig. 1B**).^{36,48,106}

Screening for SCC in the UADT by Means of Health Risk Appraisal Models

Based on the results of a case-control study,²⁰ we devised health risk appraisal (HRA) models for esophageal cancer that include ALDH2 genotype or alcohol flushing.¹⁰⁸ The total risk score is calculated by adding the scores A to E. If the risk score is 11 or more according to the HRA-flushing model (**Fig. 3**), that person's risk of esophageal cancer is in the top 10% of the study population. A cross-validation study predicted that approximately 60% of the esophageal and hypopharyngeal SCCs in the entire population could be detected by examining only people whose risk scores were in the top 10% in the HRA models (i.e., sensitivity \approx 60% and specificity \approx 90%). The esophageal SCC detection rate among Japanese men aged 40 years or older whose risk score was in the top 10% (i.e., positive predictive value, PPV) was expected to be 1%–2%. Follow-up endoscopy with esophageal iodine staining (median follow-up period: 5.0 years) was performed on 404 cancer-free controls (aged 50–78 years), and resulted in the diagnosis of six esophageal SCCs and two pharyngeal SCCs. The risk scores of six of the eight cancer patients at baseline were in the top 10% according to the HRA-flushing model.¹⁰⁹

The cancer detection rate per 100 person-years in the top 10% risk group was 2.3 for esophageal cancer and 3.5 for esophageal or pharyngeal cancer. These figures have encouraged screening with our questionnaire in larger populations of Japanese men.

We are now applying this HRA-flushing questionnaire to mass-screening programs in large Japanese populations. This questionnaire enables many people to identify their risk of UADT cancer very easily, and public awareness campaigns using the questionnaire will encourage high-risk persons to undergo endoscopic screening or convince them to change their lifestyle to prevent UADT cancer. The HRA model using ALDH2 genotyping yielded a slightly better PPV¹⁰⁸ and a slightly higher cancer detection rate¹⁰⁹ than the HRA-flushing model. An initial cost would be necessary to genotype ALDH2 in all individuals in the target population. However, it should be emphasized that genotyping needs to be performed only once in a lifetime, that the data are always available, and that the unit cost would be greatly discounted if a huge number of samples were analyzed.

Screening for SCC in the UADT Based on Red Cell MCV

A high red cell mean corpuscular volume (MCV) is a traditional biological marker for alcohol abuse and alcoholism.¹¹⁰ Recent epidemiological evidence indicates that the MCV of drinkers with *ALDH2*1/*2* increases in response to exposure to acetaldehyde.^{4,111–115} Smoking, a low BMI, and folate deficiency also increase MCV.^{113–115} MCV is used as a biomarker for risk of esophageal and

Risk factors	Risk score (select one each for A-E)	
Facial flushing and drinking (1 unit =22g ethanol)		
Any flushing		
Never/rare drinker (<1 unit/w)	0	} A
Never flushing		
Light drinker (1-8.9 units/w)	1	
Moderate drinker (9-17.9 units/w)	5	
Heavy drinker (18+ units/w)	6	
Ex-drinker	7	
Current/former flushing		
Light drinker (1-8.9 units/w)	4	
Moderate drinker (9-17.9 units/w)	9	
Heavy drinker (18+ units/w)	10	
Ex-drinker	8	
Drink strong alcoholic beverages frequently		
Yes	3	} B
No	0	
Smoked 30 pack-years or more		
Yes	2	} C
No	0	
Eat green-yellow vegetables almost every day		
Yes	0	} D
No	1	
Eat fruit almost every day		
Yes	0	} E
No	1	

Total risk score = A + B + C + D + E	
Total risk score	Predicted risk
0-2	Bottom 25%
3-5	25-49%
6-8	50-74%
9-10	75-89%
11+	Top 10%

Fig. 3 Health risk appraisal model for esophageal cancer combined with the simple flushing questionnaire. The risk score is calculated as the sum of scores A to E. The expected esophageal cancer detection rate of Japanese men 40 years of age and over with a risk score of 11 or more who undergo endoscopic screening with esophageal iodine staining is 1%–2%.^{108,109}

pharyngeal SCC in Japanese alcoholics.^{4,5,49} A high MCV of 106 fl or more, the *ALDH2*1/*2* genotype, and the *ADH1B*1/*1* genotype synergistically increase the risk of esophageal SCC in Japanese alcoholics [OR = 320 (27 to >1000)].⁴ The combination of high MCV and alcohol flushing is associated with a high risk of esophageal SCC, with an OR of 5.5 (2.2–13.8) in alcoholics. This way of estimating cancer risk can be easily applied in both public education and screening. An endoscopic follow-up study in cancer-free Japanese alcoholics revealed that cancer of the UADT developed much more frequently among alcoholics with a high MCV of 106 fl or more [HR = 2.52 (1.22–5.22)].⁵

We have demonstrated that MCV is useful as a marker for male Japanese drinkers who are at high risk of SCC in the UADT but who are not alcoholics.^{108,113,114} Combining MCV with the traditional risk factors drinking and smoking had better predictive power for esophageal and pharyngeal SCC than the combination of drinking and smoking alone.^{108,114} Approximately 30% of cancer-free Japanese men met the criterion of a combination of moderate-to-heavy drinking (≥ 198 g ethanol/week) and either 30+ pack-years or an MCV ≥ 99 fl, whereas

approximately 70% of Japanese men with SCC of the esophagus or hypopharynx met the criterion.¹⁰⁸ MCV may be used to better select not only alcoholic male Japanese candidates to screen for this high mortality cancer but non-alcoholic male Japanese candidates as well. MCV is not a predictor of esophageal cancer in Caucasian heavy drinkers, probably because the main determinant of high MCV is severe acetaldehydemia after heavy drinking in inactive *ALDH2* heterozygotes.¹¹⁶

Genetic Polymorphism of *ADH1B*, Alcohol Metabolism, and SCC in the UADT

Alcohol dehydrogenase-1B (*ADH1B*, previously called *ADH2*) also has a functional genetic polymorphism (rs1229984). A small fraction of East Asians have the less-active *ADH1B*1/*1* genotype (e.g., 7% of Japanese)¹⁵ that is prevalent in Caucasians (present in approximately 90%); this less-active *ADH1B* is a strong risk factor for alcoholism in East Asians. Approximately 30% of Japanese and Taiwanese alcoholics have the less-active *ADH1B*1/*1* genotype,^{15,54} and this genotype has been found to be more frequent in Japanese and Tai-

wanese alcoholics with cancer in the UADT^{30,31,49} [e.g., OR = 3.46 (1.66–7.22) for oropharyngolaryngeal SCC⁴⁹ and 2.64 (1.62–4.31) for esophageal SCC³¹]. An endoscopic follow-up study in Japanese alcoholics demonstrated that SCC of the UADT was more common among alcoholics with the less-active *ADH1B*1/*1* [HR = 2.07 (1.01–4.26)].⁵ With the exception of two negative Japanese studies,^{25,36} the *ADH1B*1/*1* genotype has consistently been demonstrated to be associated with an increased risk of SCC in the UADT in non-alcoholic Japanese (Fig. 1C),^{20,22,28,48,117} Chinese,^{26,27,38–41} Thai¹¹⁸ and Central European populations.¹¹⁹ Stratification according to drinking categories has shown that the *ADH1B*1/*1* genotype increases the risk of UADT cancer in light drinkers^{20,26–28,119} as well as in moderate-to-heavy drinkers.^{20,26–28,38,41,48,117,119}

The mechanism of the increase in risk of alcoholism and UADT cancer associated with the *ADH1B*1/*1* genotype has remained a puzzle. Alcohol challenge tests have failed to demonstrate any associations between *ADH1B* genotype and the blood ethanol or acetaldehyde concentration after ingestion of light to moderate doses of ethanol by Japanese,¹⁷ Chinese,¹²⁰ and Europeans.¹²¹ However, the less-active form of *ADH1B* encoded by the *ADH1B*1/*1* genotype has an approximately 40 times lower *V_{max}* *in vitro* than that encoded by *ADH1B*2/*2*,¹²² and an experiment in which a clamping technique and intravenous alcohol infusion were used showed a modestly but significantly lower ethanol elimination rate (11%–18%) among Jews with the less-active *ADH1B*1/*1* genotype than with the *ADH1B*2* allele.¹²³ Heavy drinking may amplify the modest effect of *ADH1B*1/*1* on ethanol metabolism and lead to clear prolongation of the presence of ethanol in the body, including in the UADT. Although ethical considerations make it impossible to experimentally emulate the dangerously heavy drinking found in alcoholics, many alcoholic patients come to our Alcoholism Center after drinking the day before, and they have provided an opportunity to measure blood and salivary acetaldehyde and ethanol levels in that state. When we measured the blood and salivary ethanol and acetaldehyde levels of Japanese alcoholics in the morning when they first visited our Center after drinking the day before,^{88,124} we found that ethanol and acetaldehyde remained in the blood and saliva for much longer periods and at much higher levels in those with the less-active *ADH1B*1/*1* genotype than in those with other genotypes, even after adjusting for age, body weight, the amount of alcohol consumed, and interval since the most recent drink. The blood and salivary ethanol levels were similar, but the acetaldehyde levels in saliva were strikingly higher than in the blood because of acetaldehyde production by oral microorganisms (e.g., median salivary acetaldehyde concentration of 47.4 μ M in *ADH1B*1/*1* carriers vs. 1.6 μ M in *ADH1B*2* allele carriers, *P* = 0.009).⁸⁸ However,

none of the levels differed according to *ALDH2* genotype.¹²⁴ The *ADH1B* and *ALDH2* genotypes affect the blood and salivary ethanol and acetaldehyde levels of non-abstinent alcoholics in a different manner than in non-alcoholics, and clear effects of *ADH1B* genotype and less clear effects of *ALDH2* have been observed in non-abstinent alcoholics. Alterations in alcohol metabolism as a result of alcoholism may modify the gene effects.¹²⁴

East Asians^{106,107,125–127} and Europeans¹²⁸ with the less-active *ADH1B*1/*1* genotype tend not to report alcohol flushing responses and tend to consume larger amounts of alcohol than those with the *ADH1B*2* allele. Alcohol-induced flushing is triggered by a steep initial rise in either blood or cutaneous acetaldehyde after drinking. This dramatic change may not occur in persons with the less-active *ADH1B*. The initial phase of acetaldehyde production may be difficult to monitor in conventional alcohol-challenge tests. Less-active *ADH1B*1/*1* markedly masked inactive *ALDH2*1/*2*-associated alcohol flushing. According to responses to the simple flushing questionnaire, 53% of alcoholics with cancer who had the combination of inactive *ALDH2*1/*2* and less-active *ADH1B*1/*1* were never flushers¹⁰⁷; 28% of cancer-free Japanese men with this genotype combination reported never flushing, 38% reported former flushing, and only 37% reported current flushing.¹⁰⁶ The levels of alcohol consumption by inactive *ALDH2* heterozygotes were clearly associated with their alcohol flushing categories.¹⁰⁶

The above findings provide a clue as to why less-active *ADH1B* increases the risk of both alcoholism and UADT cancer. First, less-active *ADH1B* diminishes the intensity of alcohol flushing, thereby accounting for the greater susceptibility to alcoholism associated with it. Second, heavy drinking by alcoholics amplifies the modest effect of less-active *ADH1B* on ethanol elimination, which leads to much longer exposure to ethanol and, in turn, results in smelling of alcohol in the morning. When ethanol lingers in the body, the UADT is exposed to high levels of acetaldehyde as a result of acetaldehyde production in saliva, and that creates a condition that increases the risk of UADT cancer (Fig. 4).

The increase in risk of UADT cancer associated with the inactive *ALDH2*1/*2* genotype in Japanese alcoholics is higher than the increase associated with the less-active *ADH1B*1/*1* genotype.^{5,31,49} Only the inactive *ALDH2*1/*2* genotype, and not the less-active *ADH1B*1/*1* genotype, increases the risk of synchronous and metachronous multiple UADT cancers in Japanese alcoholics.^{50,59} The high tissue accumulation of acetaldehyde in alcoholics with the *ALDH2*1/*2* genotype may affect the risk of SCC in the UADT differently from the prolonged exposure of the UADT to ethanol and acetaldehyde in alcoholics with the *ADH1B*1/*1* genotype.

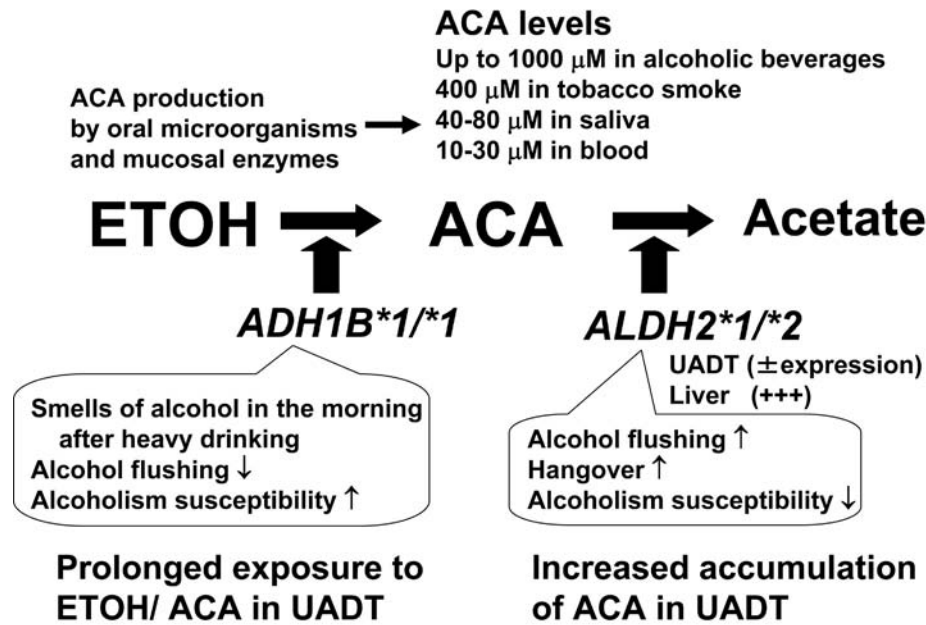


Fig. 4 Ethanol (ETOH) and acetaldehyde (ACA) exposure and accumulation in the upper aerodigestive tract (UADT) and the effects of *alcohol dehydrogenase-1B*1/*1* (*ADH1B*1/*1*) and *aldehyde dehydrogenase-2*1/*2* (*ALDH2*1/*2*) genotypes.

Combination of *ADH1B* and *ALDH2* Genotypes and SCC in the UADT

The risk of SCC in the oropharyngolarynx and esophagus in Japanese alcoholics has been found to be greatly increased in a multiplicative fashion by the combination of less-active *ADH1B*1/*1* and inactive *ALDH2*1/*2* [OR = 122 (32–465) and 40 (18–91), respectively].³¹ The PAR due to all combinations of *ADH1B* and *ALDH2* genotypes in the alcoholic population has been found to be 82% for oropharyngolaryngeal SCC and 64% for esophageal SCC. Case-control studies in a general population confirmed a similar multiplicative effect of this genotype combination on the risk of SCC of the esophagus²⁰ and hypopharynx⁴⁸ in Japanese subjects and on the risk of SCC of the esophagus in Taiwanese subjects²⁶ [OR = 30.1 (13.2–68.9), 48.9, and 36.8 (9.4–144.7), respectively]. When the presence of these two genotypes was combined with consumption of 198–395 g ethanol/week or ≥ 396 g ethanol/week, the OR for esophageal SCC was estimated to be 248 and 417, respectively, in Japanese based on the multivariate OR for each risk factor.²⁰ A Taiwanese study also showed a multiplicative effect among the less-active *ADH1B*, inactive *ALDH2*, and drinking of more than 30 g ethanol/day [OR = 382 (47–3085)].²⁷ A Japanese genome-wide association study of esophageal SCC showed that individuals with both high-risk genotypes who smoked and drank >96.5 g ethanol/week had a 189 (95–377) times higher risk of esophageal SCC than those who had none of these risk factors.²⁸

Genetic Polymorphism of *ADH1C*, Alcohol Metabolism, and SCC in the UADT

The enzyme encoded by the *ADH1C*1* allele (previously called *ADH3*1*) catalyzes acetaldehyde production twice as fast as the enzyme encoded by the *ADH1C*2* allele (rs1693482 and rs698).¹²² The *ADH1C*2* allele has been reported to increase the risk of alcoholism in East Asians^{15,54} and of both UADT cancer^{20,48} and multiple iodine-unstained lesions⁵⁸ in Japanese drinkers. However, the associations with *ADH1C* were explained by linkage disequilibrium in which the *ADH1C*2* allele and the more influential *ADH1B*1* allele are linked; the associations disappeared after adjustment for the linkage.^{15,20,48,54} A cross-sectional study in 2299 non-alcoholic Japanese subjects showed a significant positive association between the presence of an *ADH1C*2* allele and habitual drinking, regardless of the *ADH1B* genotype; however, the impact on habitual drinking was weak (3%–16% increase in OR).¹²⁹

ADH1C polymorphism may be the rate-limiting factor in acetaldehyde metabolism in Western populations, in which the prevalence of the *ALDH2*2* allele and *ADH1B*2* allele is very low. Caucasians with the high-activity *ADH1C*1/*1* genotype have been found to have significantly higher salivary acetaldehyde concentrations after alcohol ingestion than *ADH1C*2* allele carriers.¹³⁰ Although published studies have not shown a consistent pattern of association,¹³¹ several Western studies have shown that individuals in heavy drinking populations who had the *ADH1C*1* allele were at greater risk for UADT cancer.^{130,132,133}

SCC in the UADT in Ex-drinkers

A recent pooled analysis including 13 studies and over 5000 cases demonstrated that the risk of esophageal cancer and risk of head and neck cancer only started to decline 5 years and 10 years, respectively, after alcohol intake ceased, probably because of the so-called “sick-quitter” effect.^{1,3,4} Two Japanese case-control studies showed a very high risk of SCC in ex-drinkers with the *ALDH2**1/*2 or *ADH1B**1/*1 genotype.^{20,48} Endoscopic follow-up studies in Japanese alcoholics after treatment of esophageal SCC failed to detect any effects of drinking cessation on the development of metachronous cancer,^{5,6,62} suggesting that the molecular changes that predispose patients to metachronous cancer might be at the point of no return, and that intensive follow-up examinations are essential for cancer prevention in high-risk patients. Further study is needed to evaluate the longer-term effect of drinking cessation on the development of SCC in the UADT.

Conclusions

The ethanol in alcoholic beverages and the acetaldehyde associated with alcohol consumption are human carcinogens (Group 1, IARC). The inactive heterozygous *ALDH2**1/*2 genotype and the less-active *ADH1B**1/*1 genotype modify ethanol metabolism and greatly increase the susceptibility of the UADT to SCC in East Asian drinkers. The simple flushing questionnaire and MCV are useful tools that facilitate the assessment of ALDH2-associated cancer risk. Melanosis in the UADT and large or multiple esophageal dysplasia are endoscopic evidence of a high risk of developing SCC in the UADT. New health appraisal models that include the ALDH2 genotype, the simple flushing questionnaire, or MCV may provide powerful tools for cancer prevention and cancer screening in East Asians.

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