Chapter 15
Genetic Polymorphisms of Alcohol Dehydrogense-1B and Aldehyde Dehydrogenase-2, Alcohol Flushing, Mean Corpuscular Volume, and Aerodigestive Tract Neoplasia in Japanese Drinkers

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Abstract Genetic polymorphisms of alcohol dehydrogenase-1B (ADH1B) and aldehyde dehydrogenase-2 (ALDH2) modulate exposure levels to ethanol/acetaldehyde. Endoscopic screening of 6,014 Japanese alcoholics yielded high detection rates of esophageal squamous cell carcinoma (SCC; 4.1 %) and head and neck SCC (1.0 %). The risks of upper aerodigestive tract SCC/dysplasia, especially of multiple SCC/dysplasia, were increased in a multiplicative fashion by the presence of a combination of slow-metabolizing *ADH1B*1/*1* and inactive heterozygous *ALDH2*1/*2* because of prolonged exposure to higher concentrations of ethanol/acetaldehyde. A questionnaire asking about current and past facial flushing after drinking a glass (≈180 mL) of beer is a reliable tool for detecting the presence of inactive ALDH2. We invented a health-risk appraisal (HRA) model including the flushing questionnaire and drinking, smoking, and dietary habits. Esophageal SCC was detected at a high rate by endoscopic mass-screening in high HRA score persons. A total of 5.0 % of 4,879 alcoholics had a history of (4.0 %) or newly diagnosed (1.0 %) gastric cancer. Their high frequency of a history of gastric cancer is partly explained by gastrectomy being a risk factor for alcoholism because of altered ethanol metabolism, e.g., by blood ethanol level overshooting. The combination of *H. pylori-associated* atrophic gastritis and *ALDH2*1/*2* showed the greatest risk of gastric cancer in alcoholics. High detection rates of advanced colorectal adenoma/carcinoma were found in alcoholics, 15.7 % of 744 immunochemical fecal occult blood test (IFOBT)-negative alcoholics and 31.5 % of the 393 IFOBT-positive alcoholics.

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Macrocytosis with an MCV ≥ 106 fl increased the risk of neoplasia in the entire aerodigestive tract of alcoholics, suggesting that poor nutrition as well as ethanol/acetaldehyde exposure plays an important role in neoplasia.

Keywords Acetaldehyde • Alcohol dehydrogenase • Alcoholic • Aldehyde dehydrogenase • Colorectal neoplasia • Esophageal cancer • Head and neck cancer • Mean corpuscular volume • Stomach cancer

15.1   Endoscopy and Esophageal Iodine Staining of Screening Japanese Alcoholic Men for Upper Aerodigestive Tract Neoplasia

Alcohol consumption, tobacco smoking, inadequate intake of fruits and vegetables, and low body mass index (BMI) are risk factors for squamous cell carcinoma (SCC) of the upper aerodigestive tract (UADT, i.e., the oral cavity, pharynx, larynx, and esophagus), and many alcoholic patients have all of these risk factors. We introduced an endoscopic screening program at Kurihama Medical and Addiction Center in 1993 [1], and by 2010 initial screening of 6,014 Japanese alcoholic men by endoscopy combined with head and neck inspection and esophageal iodine staining had detected esophageal SCC in 243 (4.0 %) of them and head and neck SCC in 65 (1.1 %) of them. Barrett adenocarcinoma was detected in only two patients. Technical improvements in endoscopes and a growing understanding of the endoscopic findings of early SCC in the UADT [2, 3] have enabled very early detection of SCC in the UADT. Treatment of early SCC in UADT by endoscopic or endoscope-guided mucosectomy has become a widespread practice in Japan and succeeded in improving the outcome of this high-mortality cancer [3, 4].

15.2   ALDH2 Genotype and Alcohol Metabolism

Genetic polymorphism of aldehyde dehydrogenase-2 (ALDH2, rs671) modulates exposure levels to acetaldehyde after drinking (Fig. 15.1). A mutant *ALDH2*2* allele encoding an inactive subunit of ALDH2 was carried by Han Chinese as they spread throughout East Asia [5]. About 40 % of Japanese, 7 % being homozygotes and 35 % heterozygotes [6], have the inactive *ALDH2*2* allele which acts in a dominant manner. After drinking a small amount of alcohol, people with inactive ALDH2 tend to experience a flushing response that includes facial flushing, palpitations, nausea, and drowsiness [7]. People with inactive ALDH2 [8] or with inactive-ALDH2-associated facial flushing [9] tend to experience a hangover in the morning after drinking a smaller amount of alcohol than people without either of them. Thus presence of inactive ALDH2 in some East Asians tends to prevent them from drinking heavily [6]. Because of their very intense flushing responses *ALDH2*2/*2* homozygotes are
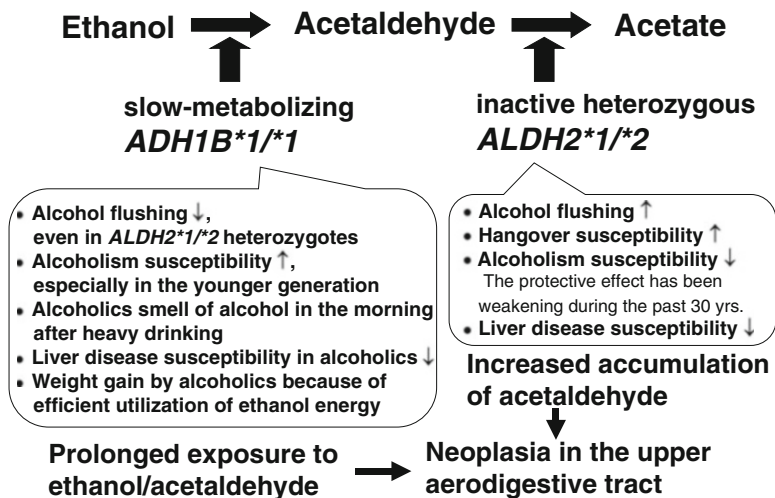
Fig. 15.1 Phenotypes of the *alcohol dehydrogenase-1B*1/*1* (*ADH1B*1/*1*) and *aldehyde dehydrogenase-2*1/*2* (*ALDH2*1/*2*) genotypes and their relationships to ethanol and acetaldehyde exposure and accumulation

usually nondrinkers or occasional drinkers. However, the inhibitory effect of being heterozygous for inactive ALDH2 on heavy drinking is influenced by sociocultural factors. The proportion of Japanese alcoholics with the *ALDH2*1/*2* genotype increased dramatically from 2.5 % in 1979, to 8.0 % in 1986, and to 13.0 % in 1992 [10], and the proportion continued to increase from 13.0 % in 1996–2000, to 14.0 % in 2001–2005, and to 15.4 % in 2006–2010 [11].

15.3   ALDH2 Genotype and Squamous Cell Neoplasia in the UADT

In 1996, we first reported that being heterozygous for inactive ALDH2 is a strong risk factor for esophageal cancer in daily drinkers and alcoholics [12]. Since then, epidemiological studies have almost consistently demonstrated a strong association between the *ALDH2*1/*2* genotype and the risk of UADT cancer in East-Asian drinkers [13]. A meta-analysis of Asian case–control studies of esophageal cancer showed that the *ALDH2*1/*2*-associated odds ratio (95 % confidence interval) [OR (95 % CI)] for esophageal cancer was 3.12 (1.95–5.02) in moderate drinkers, 5.64 (1.57–20.25) in ex-drinkers, and 7.12 (4.67–10.86) in heavy drinkers [14]. The *ALDH2*1/*2* genotype has been found to be a very strong risk factor for esophageal cancer among Taiwan Chinese and Japanese drinkers (OR=4.74–6.21 in moderate drinkers and 9.21–9.75 in heavy drinkers), but the OR associated with the *ALDH2*1/*2* genotype in the high incidence regions of esophageal cancer of Mainland China was not so high (OR=1.98 in moderate drinkers and 1.31 in heavy

drinkers). The meta-analysis confirmed that being homozygous for the inactive allele, i.e., having the *ALDH2*2/*2* genotype greatly increased the risk of esophageal cancer in drinkers, and that the heterozygous genotype, i.e., *ALDH2*1/*2* increased the risk of esophageal cancer in a similar manner in both men and women. A meta-analysis of 6 Japanese case–control studies showed that the *ALDH2*1/*2-associated* risk for head and neck cancer was also greater in heavy drinkers [OR (95 % CI) = 3.57 (1.21–2.77)] than in moderate drinkers [OR (95 % CI) = 1.68 (1.22–2.27)] [15].

The United States National Cancer Institute's SEER Program reported synchronous multiple cancers and metachronous multiple cancers in only 2 % and 3 %, respectively, of esophageal cancer patients during the 1973–2003 period [16]. The prevalence of multiple organ cancers among esophageal cancer patients treated at the National Cancer Center of Japan increased at an alarming rate between 1969 and 1996 from 6.3 % in 1969–1980, to 22.2 % in 1981–1991, and to 39.0 % in 1992–1996 [17], and the most frequent sites of the other cancers were the head and neck and stomach. The increased proportion of multiple cancers in Japanese esophageal cancer patients may partly explained by a dramatic increase in the proportion of *ALDH2*1/*2* heterozygotes among Japanese heavy drinkers during the same period [10]. The *ALDH2*1/*2* genotype has consistently been demonstrated to be a strong determinant of the risk of synchronous and metachronous SCC of the UADT in Japanese drinkers [13].

The ORs (95 % CI) associated with the *ALDH2*1/*2* genotype in Japanese alcoholics has been found to increase for the very early stages of the esophageal neoplasia, from 2.88 (1.81–4.57) for low-grade intraepithelial neoplasia, to 5.14 (2.87–9.19) for high-grade intraepithelial neoplasia, and to 4.07 (1.97–8.40) for invasive SCC [18]. The presence of multiple esophageal iodine-unstained lesions or a large esophageal dysplasia has been found to be a strong predictor of the development of multiple cancers in the UADT in Japanese [13], and to be associated with the *ALDH2*1/*2* genotype [18], p53 alteration [19], and telomere shortening in the esophagus [20] in Japanese alcoholics. Thus, acetaldehyde, which is an established human carcinogen, plays a critical role in the multicentric development of neoplasia throughout the UADT.

15.4 The Simple Flushing Questionnaire

The discovery of ALDH2-associated cancer susceptibility emphasizes the importance of developing screening tests for inactive ALDH2 based on alcohol flushing. We devised a flushing questionnaire to identify person with inactive ALDH2 (Fig. 15.2) [21, 22]. 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? The results are used to classify the subjects as a current flusher, former flusher, or
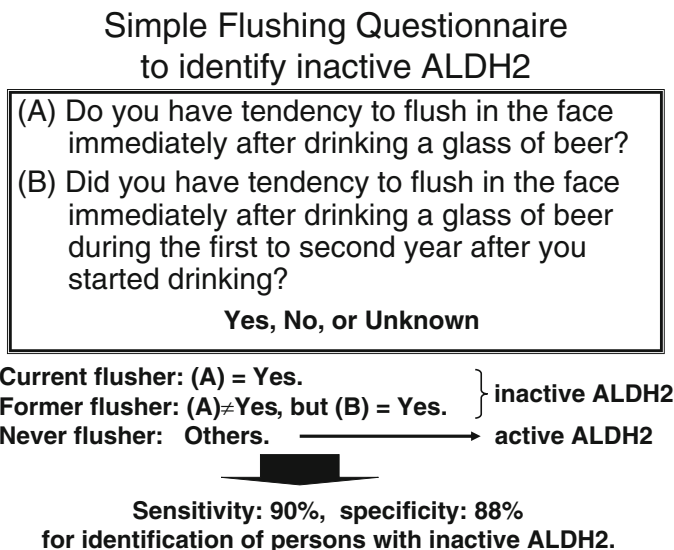
Simple Flushing Questionnaire
to identify inactive ALDH2

(A) Do you have tendency to flush in the face immediately after drinking a glass of beer?

(B) Did you have tendency to flush in the face immediately after drinking a glass of beer during the first to second year after you started drinking?

Yes, No, or Unknown

Current flusher: (A) = Yes.
Former flusher: (A)≠Yes, but (B) = Yes. ⎫ **inactive ALDH2**
Never flusher: Others. ⟶ **active ALDH2**

Sensitivity: 90%, specificity: 88%
for identification of persons with inactive ALDH2.

Fig. 15.2 The simple flushing questionnaire to identify persons with inactive ALDH2. Sensitivity and specificity are both approximately 90 % in Japanese 40 years of age and over, regardless of gender

never flusher. When current flushers or former flushers were assumed to have inactive ALDH2, the simple flushing questionnaire had 90 % sensitivity and 88 % specificity when evaluated in 610 Japanese men 40 years of age or older [22] and 88 % sensitivity and 92 % specificity when evaluated in 381 Japanese women 40 years of age or older [23]. The individuals' risks of UADT cancer estimated on the basis of the replies to the flushing questionnaire were slightly lower than but essentially comparable to their risks estimated on the basis of ALDH2 genotyping [21–23].

15.5 Mass-Screening for SCC of the UADT by Means of Health-Risk Appraisal Models

Based on the results of a case–control study [24], we devised health-risk appraisal (HRA) models for esophageal cancer that include ALDH2 genotype or alcohol flushing [25]. The total risk score is calculated by adding the scores A–E (Fig. 15.3). If a person's risk score is 11 or more according to the HRA-Flushing model, 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. Follow-up endoscopy with esophageal iodine staining (median follow-up period: 5.0 years)

Factors	Risk score (select one choice each for A-E)

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

Total risk score = A + B + C + D + E

High -risk scores
Endoscopic screening
is recommended

Age 50-69 years   9 or more

Age ≥70 years   8 or more

Fig. 15.3 Health-risk appraisal model for esophageal cancer combined with the simple flushing questionnaire. The questionnaire enables makes it possible for people to easily determine their risk of esophageal cancer, and public awareness campaigns that use the questionnaire will help persuade high-risk persons to undergo endoscopic screening or enable them to change their lifestyle to prevent esophageal cancer

was performed on 404 cancer-free controls and resulted in the diagnosis of six esophageal SCCs and two pharyngeal SCCs [26]. The risk scores of six of these eight cancer patients at baseline were in the top 10 % according to the HRA-Flushing model. The cancer detection rate per 100 person–years in the top 10 % risk group of the cancer-free controls was 2.3 for esophageal cancer and 3.5 for esophageal or pharyngeal cancer. We applied this HRA-Flushing questionnaire to endoscopic mass-screening programs of 2,221 Japanese men during 2008 and 2009 at five cancer screening facilities, and esophageal cancer was diagnosed in 19 persons as a result [27]. The HRA-Flushing score of 5 % of the examinees was 11 or greater, and esophageal cancer was detected in 4.3 % of them, as opposed to in 0.7 % of the other examinees. A receiver operating characteristic curve analysis showed that when we used an cutoff point of an HRA score of ≥9 in the 50–69 age group and of ≥8 in the 70–89 age group to select individuals with a high risk for esophageal cancer, the sensitivity and false-positive rate was 52.6 % and 15.2 %, respectively, and cancer was detected in 2.91 % of the examinees in the high-risk group, as opposed to 0.48 % in the other group. Although the cutoff values for high-risk groups should

be changed to achieve better performance of the HRA model according to the population targeted, these figures encouraged using our questionnaire to screen larger populations of Japanese men.

Our simple questionnaire makes it possible for many people to identify their risk of UADT cancer very easily, and use of the questionnaire in public awareness campaigns will help persuade high-risk persons to undergo endoscopic screening or enable them to change their lifestyle to prevent UADT cancer. Our HRA model that includes ALDH2 genotype yielded a slightly better positive predictive value [25] and a slightly higher cancer detection rate [26] than the HRA-Flushing model. Genotyping ALDH2 would entail an initial cost, but genotyping needs to be performed only once in a lifetime, the data are always available, and the unit cost would be greatly discounted if a huge number of samples are analyzed.

15.6 ADH1B Genotype, Alcohol Metabolism, and SCC of the UADT

Alcohol dehydrogenase-1B (ADH1B, previously called ADH2) also has a functional genetic polymorphism (rs1229984; Fig. 15.1). The *ADH1B*1/*1* genotype, which results in expression of slow-metabolizing ADH1B, is prevalent in Caucasians (present in approximately 90 %), but present in only a small fraction of East Asians (e.g., 7 % of Japanese) [6]. The presence of slow-metabolizing ADH1B is a stronger risk factor for alcoholism and SCC of the UADT in East Asians than the presence of the fast-metabolizing ADH1B because of having the *ADH1B*2* allele. Approximately 30 % of Japanese alcoholics have the slow-metabolizing ADH1B, and the slow-metabolizing ADH1B has been found to be more frequent in the younger generations of Japanese alcoholics, probably because the *ADH1B*1/*1* genotype accelerates the progression of alcohol dependence [11].

Alcohol challenge tests have failed to demonstrate any associations between ADH1B genotype and the blood ethanol or acetaldehyde concentrations after ingestion of small to moderate doses of ethanol [13]. However, the slow-metabolizing ADH1B has an approximately 40 times lower Vmax in vitro than the fast-metabolizing ADH1B [28], 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 slow-metabolizing ADH1B than with the fast-metabolizing ADH1B [29]. At the time of their first visit to our Addiction Center, we evaluated associations between ADH1B and ALDH2 genotypes and the blood ethanol levels of 805 Japanese alcoholic men in the morning after drinking within the previous 34 h [30]. The results showed no significant differences in age-adjusted usual alcohol consumption according to ADH1B or ALDH2 genotypes. Higher blood ethanol levels persisted for longer periods in the group with the slow-metabolizing ADH1B who were *ADH1B*1/*1* carriers ($n=246$) than in the group with the fast-metabolizing ADH1B who were *ADH1B*2* carriers ($n=559$), and blood ethanol levels ≥0.3 mg/mL (criterion for drunk driving

according to Japanese law) after a 12.1–18-h interval since the last drink were observed in a significantly higher proportion of the *ADH1B*1/*1* carriers than of the *ADH1B*2* carriers (40 % vs. 14–17 %, *p* < 0.0001). Multivariate analyses showed that the ethanol levels were 0.500 mg/mL higher in the group with the *ADH1B*1*1* genotype, and the OR (95 % CI) for an ethanol level ≥0.3 mg/mL in the presence of the *ADH1B*1/*1* genotype was 3.44 (2.34–5.04). There were no significant differences in blood ethanol levels according to ALDH2 genotype.

We evaluated associations between ADH1B and ALDH2 genotypes and the body weight and BMI of 1,301 Japanese alcoholic men on the day of their first visit [31]. There were no significant differences in usual caloric intake in the form of alcoholic beverages according to ADH1B genotype in any of the age brackets, but the presence of the slow-metabolizing ADH1B was more strongly associated with weight gain in all age brackets. This result links the slower ethanol elimination by the *ADH1B*1*/*1* alcoholics with their more efficient utilization of ethanol as an energy source. No effects of ALDH2 genotype on body weight or BMI were observed.

In a study in which we simultaneously measured the blood and salivary ethanol and acetaldehyde levels of Japanese alcoholics in the morning on the day of their first visit [32, 33], we found that ethanol and acetaldehyde remained in the blood and saliva for much longer periods and at much higher levels in the group with the slow-metabolizing ADH1B than in the group with the fast-metabolizing ADH1B, even after adjusting for age, body weight, the amount of alcohol consumed, and interval since the previous drink. Chronic heavy drinking by alcoholics 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. The blood and salivary ethanol levels of the subjects were similar, but the acetaldehyde levels in their saliva were much higher than in their blood because of acetaldehyde production by oral microorganisms. [32, 33]

ADH1B genotype markedly affects alcohol flushing [22, 34]. Alcohol flushing in fast-metabolizing ADH1B carriers is triggered by a rapid initial rise in the blood acetaldehyde concentration, whereas the slow initial rise in the blood acetaldehyde in slow-metabolizing ADH1B carriers may weaken the alcohol flushing [22, 34]. The results of our flushing questionnaire showed that despite the presence of inactive ALDH2 in heterozygotes, 25 % of the slow-metabolizing ADH1B carriers were never flushers and 38 % were former flushers, and thus there was a clear association between alcohol consumption by inactive ALDH2 heterozygotes and their facial flushing categories [22].

The above findings provide clues as to why slow-metabolizing ADH1B increases the risk of both alcoholism and UADT cancer. First, slow-metabolizing ADH1B diminishes the intensity of facial flushing, thereby accounting for the greater susceptibility to heavy drinking. Second, chronic heavy drinking amplifies the modest effect of slow-metabolizing ADH1B on ethanol elimination, which leads to much longer exposure to ethanol and, in turn, results in increasing the risk of developing alcoholism. 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.

15.7 The *ADH1B*1/*1* and *ALDH2*1/*2* Genotype Combination and SCC in the UADT

The risk of SCC of the head and neck and esophagus of Japanese and Taiwanese drinkers has been found to be extremely increased in a multiplicative fashion by the combination of slow-metabolizing ADH1B in the *ADH1B*1/*1* genotype and inactive ALDH2 in the *ALDH2*1/*2* genotype (OR = 22–122 for esophageal SCC) [13, 18, 24, 35–37]. In Japanese alcoholics, the OR (95 % CI) with the *ADH1B*1/*1* and *ALDH2*1/*2* genotype combination has been found to increase for the very early stages of the esophageal neoplasia, from 4.53 (2.17–9.47) for low-grade intraepithelial neoplasia, to 10.4 (4.34–24.7) for high-grade intraepithelial neoplasia, and 21.7 (7.96–59.3) for invasive SCC [18]. When the two genotypes were combined with other risk factors, based on the multivariate OR for each risk factor the ORs (95 % CI) of Japanese for esophageal SCC increased enormously, by 248 times when combined with consumption of 198–395 g ethanol/week and by 414 times when combined with consumption of ≥396 g ethanol/week [24], in Taiwanese by 382 (47–3,085) times when combined with consumption of >30 g ethanol/day [35], and in Japanese by 189 (95–377) times when combined with both consumption of >96.5 g ethanol/week and smoking [36] and by 357 (105–1,210) times when combined with both drinking and smoking [37].

15.8 ADH1B and ALDH2 Genotype and Liver Disease in Japanese Alcoholic Men

Contrary to results of investigations of the relationships between the ADH1B and ALDH2 genotypes and susceptibility to UADT cancer, a cross-sectional survey of 1,902 Japanese alcoholic men showed that liver cirrhosis was associated with the presence of the *ADH1B*2* allele and *ALDH2*1/*1* genotype [38]. When non-cirrhotic patients with no or only mild liver fibrosis as controls, the results showed that the OR (95 % CI) of the *ADH1B*2* allele increased according to the severity of their liver disease, from 1.67 (1.32–2.11) in the non-cirrhotic group with liver fibrosis, to 1.81 (1.24–2.63) in the Child-Pugh class A cirrhosis group, 2.97 (1.79–4.93) in the Child-Pugh class B cirrhosis group, and 4.32 (1.48–12.6) in the Child-Pugh class C cirrhosis group. Since age-adjusted daily alcohol consumption did not differ according to ADH1B/ALDH2 genotypes in the alcoholics, their ADH1B/ALDH2-associated increase in risk of liver disease cannot be explained by the levels of ethanol and acetaldehyde exposure.

15.9 Gastric Cancer in Japanese Alcoholic Men

The lifetime drinking profiles of Japanese alcoholic men have shown that gastrectomy increases susceptibility to alcoholism [39]. Gastrectomy results in swift passage of ethanol from the small intestine into the systemic circulation. Because of

this dynamic change in ethanol delivery, overshoot of blood ethanol levels and subsequent high ethanol exposure have been observed after gastrectomy [40], and they lead to rapid development of alcohol dependence. A large survey of 4,879 Japanese alcoholic men demonstrated that a high proportion of them had a history of gastrectomy, although the proportion decreased from 13.3 to 7.8 % during the 1996–2010 period [11]. Many alcoholic men with a history of gastrectomy had changed their drinking pattern after the gastrectomy and had became alcoholics after a shorter period of heavy drinking and after a lower cumulative alcohol intake than alcoholics with no history of gastrectomy [39]. There were more frequent blackouts in the gastrectomy group, and that may have reflected the sharper rise in their blood ethanol level. Since a history of gastrectomy increases the risk of alcohol dependence, this acquired risk factor increases susceptibility to alcohol dependence in the absence of the alcoholism-susceptibility genotype *ADH1B*1/*1*, and that explains the lower frequency of *ADH1B*1/*1* that was found in a gastrectomy group of Japanese alcoholic men than in a non-gastrectomy group [11].

The prevalence of gastric cancer is extremely high among Japanese alcoholic men. A study of 4,879 Japanese male alcoholic patients revealed that 187 had a history of gastrectomy for gastric cancer and ten had a history of mucosectomy for gastric cancer, and 47 were diagnosed with gastric cancer during the initial endoscopic screening [11]. A total of 244 (5.0 %) of the patients had a history of gastric cancer or were newly diagnosed with gastric cancer.

Inactive ALDH2, macrocytosis, and simultaneous presence of UADT cancer as well as *H. pylori*-associated atrophic gastritis have been found to be associated with the risk of gastric cancer detected by endoscopic screening of Japanese alcoholic men [41]. This finding partly explains why gastric, esophageal, and head and neck cancers are often concurrent in Japanese alcoholic men. However, the frequency of the *ALDH2*1/*2* genotype in alcoholics with a history of gastrectomy for gastric cancer was found to be as low as in alcoholics without a history of gastrectomy [11]. These findings suggest different causal associations between alcoholism and each group of gastric cancer.

The risk of metachronous gastric cancer is high in Japanese with esophageal SCC, especially among alcoholic men, suggesting a common cause of both cancers. Endoscopic follow-up (median, 47 months) after the initial diagnosis of esophageal SCC was performed in 99 Japanese alcoholic men [42]. A serum pepsinogen test showed a higher seroprevalence of severe chronic atrophic gastritis among the esophageal SCC cases than among age-matched alcoholic controls, whereas their *H. pylori* status was similar. The accelerated progression of severe chronic atrophic gastritis observed in Japanese alcoholic men with esophageal SCC suggests the existence of a common mechanism by which both esophageal SCC and *H. pylori-related* severe chronic atrophic gastritis develop in the alcoholics. Metachronous gastric adenocarcinoma was diagnosed in 11 of the 99 gastric cancer-free patients in the same study, and the cumulative rate of metachronous gastric cancer within 5 years was estimated to be 15 %. The hazard ratio [HR (95 % CI)] of metachronous gastric cancer was 7.87 (1.43–43.46) in the group with severe chronic atrophic gastritis in comparison with the group without chronic atrophic gastritis. Inactive heterozygous

ALDH2 was not associated with an increased risk of metachronous gastric cancer. Accelerated development of severe chronic atrophic gastritis at least partially explained the very high frequency of development of metachronous gastric cancer in this population of Japanese men with an initial diagnosis of SCC of the esophagus.

15.10   Colonoscopic Screening of Japanese Alcoholic Men for Colorectal Neoplasia

The results of colonoscopic screening of Japanese alcoholic men for colorectal neoplasia yielded an extremely high rate of advanced colorectal neoplasia: 15.7 % in the group of 744 subjects with a negative immunochemical fecal occult blood test (IFOBT) and 31.6 % in the group of 393 subjects with a positive IFOBT [43]. Advanced colorectal neoplasia has been reported to have been detected in 2.6 % of an IFOBT-negative group and 16.0 % of an IFOBT-positive group in the Japanese general population [44]. Advanced colorectal neoplasia includes adenomas ≥10 mm, villous and tubulovillous adenomas, high-grade dysplasia, carcinoma-in-situ, and invasive cancers. Thus, screening alcoholic men by the IFOBT alone is inadequate, and colonoscopy should be recommended to the patients. There were no significant associations between ALDH2 genotypes and the risk of advanced colorectal neoplasia [43].

15.11   Association Between a High Mean Corpuscular Volume and Increased Risk of Aerodigestive Tract Neoplasia in Japanese Alcoholic Men

Epidemiological evidence indicates that the red cell mean corpuscular volume (MCV) of inactive ALDH2 carriers is increased by exposure to acetaldehyde [45–51]. Alcoholism, severe acetaldehyde exposure because of the presence of inactive ALDH2, smoking, low BMI, and folate deficiency are associated with both increased MCV and increased risk of aerodigestive tract cancer. The simultaneous presence of a high MCV of 106 or more, *ALDH2*1/*2* genotype, and *ADH1B*1/*1* genotype in Japanese alcoholic men synergistically increase their risk of esophageal SCC [OR (95 % CI)=320 (27–>1,000)] [47]. An endoscopic follow-up study of cancer-free Japanese alcoholics revealed that cancer of the UADT developed much more frequently among alcoholics with a high MCV of 106 or more [HR (95 % CI)=2.52 (1.22–5.22)] [51]. An MCV of 106 or more in Japanese alcoholic men was found to increase their risks of head and neck SCC [OR (95 % CI)=2.71 (1.42–5.16)] [52], esophageal SCC [OR (95 % CI)=3.68 (1.96–6.93)] [48], and gastric cancer [OR (95 % CI)=2.5 (1.2–5.2)] [41], and to increase their risk of advanced colorectal neoplasia in an IFOBT-negative group [ORs (95 % CI)=1.65 (1.02–2.64)] and an IFOBT-positive group [2.83 (1.15–6.93)] [43] (Table 15.1).

Table 15.1 Age-adjusted odds ratios for aerodigestive neoplasia and high MCV in Japanese alcoholic men

MCV ≥ 106 fl	Controls	Head and neck cancer [52]	Controls	Esophageal cancer [48]
	N=215	N=43	N=206	N=65
Frequency	23 %	50 %	17 %	43 %
OR (95 % CI)	1 reference	2.71 (1.42–5.16)	1 reference	3.68 (1.96–6.93)
MCV ≥ 106 fl	Controls	Stomach cancer [41]	Controls	Advanced colorectal neoplasia [43]
	N=281	N=45	N=400	N=241
Frequency	20 %	38 %	22 %	32 %
OR (95 % CI)	1 reference	2.5 (1.2–5.2)	1 reference	1.65 (1.02–2.64)[a]
				2.83 (1.15–6.93)[b]

[a]Immunochemical fecal occult blood test negative subjects

[a]Immunochemical fecal occult blood test positive subjects

15.12   Conclusions

- The *ADH1B*1/*1* genotype and *ALDH2*1/*2* genotype are associated with an increased risk of UADT neoplasia in East-Asian drinkers.
- Prolonged exposure to high ethanol and acetaldehyde concentrations and inefficient degradation of acetaldehyde in the UADT explains the high risk of UADT neoplasia in people with these genotypes.
- Health-risk appraisal models that include alcohol flushing or ALDH2 genotype are useful tools for mass-screening for UADT neoplasia.
- The ADH1B genotype of Japanese alcoholic men affects their body weight and susceptibility to liver disease.
- Gastric cancer and advanced colorectal neoplasia are more common in Japanese alcoholic men than in nonalcoholic Japanese men.
- A high MCV in Japanese alcoholic men increases their risk of aerodigestive tract neoplasia.

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