# Multiple Cancers Associated with Esophageal and Oropharyngolaryngeal Squamous Cell Carcinoma and the *Aldehyde Dehydrogenase-2* Genotype in Male Japanese Drinkers[1]

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## Abstract

**Aldehyde dehydrogenase-2 (ALDH2) is a key enzyme for the elimination of acetaldehyde, an established animal carcinogen generated by alcohol metabolism. In the presence of *ALDH2*2*, a mutant allele that is prevalent in East Asians, this enzyme is inactive, leading to excessive accumulation of acetaldehyde. Only among Japanese alcoholic patients has the positive association between this inactive form of ALDH2 and multiple-field cancerization in the upper aerodigestive tract been demonstrated. Whether this finding could be extended to multiple-cancer patients in general is of great interest, because the prevalence of esophageal cancer with other organ cancers has increased dramatically during recent decades in Japan. This study compared the *ALDH2* genotypes of groups of male Japanese drinkers who had either esophageal squamous cell carcinomas (SCCs) with ($n = 26$) or without ($n = 48$) multiplicity or oropharyngolaryngeal SCCs with ($n = 17$) or without ($n = 29$) multiplicity. After adjustments for age and drinking and smoking habits, logistic regression analysis showed significantly increased risk for each multiplicity associated with either esophageal or oropharyngolaryngeal SCCs in the presence of the *ALDH2*2* allele (odds ratio, 5.26; 95% confidence interval, 1.08–51.06 and odds ratio, 7.36; 95% confidence interval, 1.29–80.70, respectively). This study is the first to strongly link inactive *ALDH2* with the multiple cancer susceptibility of male Japanese drinkers with either esophageal or oropharyngolaryngeal cancers. A simple questionnaire about both current and past facial flushing after drinking a glass of beer was highly sensitive (95.6%) in detecting inactive *ALDH2* in these patients and may be useful for identifying high-risk patients.**

## Introduction

The increasing prevalence of synchronous or metachronous multiple cancers in other organs (primarily in the head and neck and stomach) of overall patients undergoing surgery at Japan's National Cancer Center Hospital for esophageal cancer from 6.3% (27 of 431) in the 1969–1980 period to 22.2% (128 of 577) in 1981–1991, to 39.0% (146 of 374) in 1992–1996 (1) has been alarming. One reason for this increase is recent progress in diagnosis and treatment, which has improved the survival rates of patients with these cancers, which also enhances their chances of developing other primary cancers. Another possible explanation is that widespread use of iodine staining to screen for esophageal cancer in oropharyngolaryngeal cancer patients in Japan has detected extremely high (5.1–26.7%) rates of esophageal cancer (1, 2). However, no one can adequately explain the reasons for such a steep rise in multiple cancers among Japanese esophageal cancer patients.

Drinking alcohol and smoking synergistically increase the risks for development of cancers of the esophagus and the oropharyngolaryngeal area (3, 4). Cancers at these sites are frequently multiple, and drinking and smoking habits are important predictors of their development (5, 6). Studies of various Japanese drinking populations have shown that the inactive form of ALDH2,[3] which is encoded by the gene *ALDH2*1/2*2*, is a strong risk factor for esophageal (7–13) and oropharyngolaryngeal cancer (10, 12, 14). Whether they are every-day drinkers (7), heavy drinkers (13), or alcoholics (12), persons with the *ALDH2*1/2*2* genotype have similarly high odds of getting esophageal cancer (ORs, 12.1, 16.5, and 13.5, respectively). Among Japanese alcoholics with esophageal cancer, multiple intraesophageal cancers (12, 15, 16) and esophageal cancer concurrent with oropharyngolaryngeal and/or stomach cancer (12, 15) occur more frequently in those with the inactive ALDH2 than in those who have the active form of the enzyme. Chinese alcoholics with inactive ALDH2 also are susceptible to esophageal cancer (17).

ALDH2 is a key enzyme in the elimination of acetaldehyde, which is generated by alcohol metabolism (18). In persons with *ALDH2*2*, a mutant allele that is prevalent in East Asians, the activity of this enzyme is considerably low. This

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[3] The abbreviations used are: ALDH2, aldehyde dehydrogenase-2; SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval; $ADH_2$, alcohol dehydrogenase-2.

lower enzyme activity leads to excessive accumulation of acetaldehyde (18, 19), an established animal carcinogen (20, 21). The evidence points to a role for acetaldehyde in cancerization of the upper aerodigestive tract in male drinkers who have the inactive form of ALDH2.

Inactive ALDH2 generally inhibits East Asians from heavy drinking by causing acetaldehydemia and alcohol flushing responses, which include facial flushing, tachycardia, and drowsiness (22). The preventive effect of heterozygous *ALDH2*1/2*2* is incomplete, however, and it is influenced by sociocultural factors (23). In addition to a rapid increase in Japanese per capita alcohol consumption, recent decades have seen a dramatic increase in the proportion of heavy drinkers who have inactive heterozygous ALDH2. For example, 2.5% (10 of 400) of Japanese alcoholics had the inactive heterozygous ALDH2 in 1979, 8.0% (32 of 400) in 1986, and 13.0% (65 of 500) in 1992 (23). This phenomenon may partly explain the increased proportion of multiple cancers in Japanese esophageal cancer patients in recent decades.

Only among alcoholic patients has the positive association between inactive ALDH2 and multiple-field cancerization in cases of esophageal cancer been demonstrated (12, 15, 16). Whether this finding can be extended to non-alcoholic people is an urgent question with implications for prevention of those cancers in the general population. Should inactive ALDH2 and acetaldehyde prove to be associated with multiple-cancer cases among the general population, the knowledge will enhance the importance of developing screening tests for inactive ALDH2 based on alcohol flushing responses. Our simple flushing questionnaire has high sensitivity for detecting inactive ALDH2 in Japanese men ≥50 years of age (24). Whether it can be applied reliably in patients with esophageal or oropharyngolaryngeal cancer has not been demonstrated.

Addressing these questions, we designed this study to: **(***a***)** to assess the roles of inactive ALDH2 and other environmental factors on multiple field cancerization associated with esophageal and oropharyngolaryngeal cancer in Japanese patients treated at the National Cancer Center, where the patients were derived from Japanese general populations; and **(***b***)** evaluate the reliability of the simple flushing questionnaire in detecting inactive ALDH2 in these patients.

## Materials and Methods

The participants in this study were 110 male Japanese patients with primary esophageal or oropharyngolaryngeal SCC that was treated at the National Cancer Center Hospital and the National Cancer Center Hospital East in 1998 and 1999. They were inpatients in the charge of the coauthors. Only 1 of 111 patients who was fully informed by the coauthors of the purpose of the study refused to participate. The proposed study was reviewed and approved by the ethics committee of the National Cancer Center, and informed consent was obtained from each participating patient.

All participants independently completed a structured questionnaire concerning drinking and smoking habits. Each patient was first asked to classify himself as a never drinker, a current drinker, or an ex-drinker. After the exclusion of three patients who reported never drinking, the study analyses included 107 patients whose alcohol intake was reported as the frequency of consumption and the usual amount(s) and type(s) of alcoholic beverage(s) consumed. Daily ethanol consumption was then calculated, using a standard conversion for alcoholic beverages in which beer was considered to be 5% ethanol (v/v); wine, 12%; sake, 16%; shochu, 25%; and whiskey, 40%.

*Table 1* Solitary and multiple cancers among 107 patients with esophageal or oropharyngolaryngeal SCCs

| Cancer, site, and multiplicity | *n* |
|---|---|
| Esophageal, solitary | 48 |
| Oropharyngolaryngeal, solitary, including: | 29 |
| Hypopharynx | 9 |
| Tongue | 9 |
| Oral cavity (except tongue) | 5 |
| Oropharynx | 4 |
| Larynx | 2 |
| Intraesophageal, multiple primary | 5 |
| Esophageal, solitary, with primary cancer in other organs: | 19 |
| Stomach | 6 |
| Hypopharynx | 5 |
| Oropharynx | 2 |
| Larynx | 1 |
| Tongue | 1 |
| Thyroid | 1 |
| Bladder | 1 |
| Oropharynx and stomach | 1 |
| Oral cavity, oropharynx, hypopharynx | 1 |
| Intraesophageal, multiple primary, with primary cancer in other organs: | 2 |
| Oropharynx | 1 |
| Hypopharynx | 1 |
| Oropharyngolaryngeal, multiple primary alone, including: | 3 |
| Tongue and oral cavity | 2 |
| Nasopharynx and oropharynx | 1 |
| Tongue, solitary, with primary lung cancer | 1 |
| Total | 107 |

The presence of synchronous or metachronous multiple primary cancer was ascertained by using the subjects' medical records. Synchronous multiple primary cancers were found in 14 patients; metachronous, in 13; and both synchronous and metachronous, in 3. All of the esophageal and oropharyngolaryngeal cancers were SCCs (as listed in Table 1).

We compared the ages and smoking and drinking habits and ALDH2 status of the 48 patients who had solitary esophageal SCCs with those of the patients representing the 26 cases of multiple cancers associated with esophageal SCCs. Likewise, we compared the ALDH2 status of the 29 patients who had solitary oropharyngolaryngeal SCCs with those representing the 17 cases of multiple cancers associated with oropharyngolaryngeal SCCs. *ALDH2* genotyping of lymphocyte DNA samples from all patients was performed by a PCR-restriction fragment length polymorphism method without knowledge of the patients' cancer status (8, 25).

Each patient was also asked to fill out a simple questionnaire concerning alcohol flushing responses (24). The questions were: (*a*) Do you flush in the face immediately after drinking a glass of beer: Always, sometimes, or never? (*b*) Did you flush in the face immediately after drinking a glass of beer during the first to second year after you started drinking: Always, sometimes, or never? For reporting this study, individuals who answered "always" to the first question (*a*) are identified as "current always flushing"; those who answered "always" to the second question (*b*) but not to the first question (*a*) as "former always flushing"; and those who answered "never" to both questions as "never flushing." The remaining subjects were classified as "sometimes flushing."

The data are expressed as mean ± SD. We used the Mann-Whitney *U* test, the Mantel-extension test, or Fisher's exact test in comparing group statistics. The association between *ALDH2* genotype and multiple cancers was expressed in

*Table 2* Age, drinking, and smoking habits and *ALDH2* genotype in esophageal and oropharyngolaryngeal SCC patients with and without multiple-field cancerization

| Risk factors | Esophageal SCC | | Oropharyngolaryngeal SCC | |
|---|---|---|---|---|
| | Multiplicity absent ($n$ = 48) No. of cases | Multiplicity present ($n$ = 26)[a] No. of cases | Multiplicity absent ($n$ = 29) No. of cases | Multiplicity present ($n$ = 17)[a] No. of cases |
| Age (mean ± SD) | 63 ± 9 | 61 ± 8 | 61 ± 13 | 61 ± 10 |
| Current smokers | 29 (60.4%) | 19 (73.1%) | 23 (79.3%) | 10 (58.8%) |
| Ex-smokers | 17 (35.4%) | 5 (19.2%) | 6 (20.7%) | 5 (29.4%) |
| Never smokers | 2 (4.2%) | 2 (7.7%) | 0 (0%) | 2 (11.8%) |
| Pack-years (mean ± SD) | 46.4 ± 24.3 | 43.9 ± 26.9 | 51.4 ± 23.4 | 44.9 ± 29.7 |
| Current drinkers | 44 (91.7%) | 22 (84.6%) | 25 (86.2%) | 14 (82.4%) |
| Ex-drinkers | 4 (8.3%) | 4 (15.4%) | 4 (13.8%) | 3 (17.6%) |
| Drinks/day[b] | | | | |
| <3 | 9 (18.8%) | 3 (11.5%) | 6 (20.7%) | 3 (17.6%) |
| 3–5.9 | 17 (35.4%) | 8 (30.8%) | 6 (20.7%) | 6 (35.3%) |
| ≥6 | 18 (37.5%) | 11 (42.3%) | 13 (44.8%) | 5 (29.4%) |
| *ALDH2*1/2*1* | 16 (33.3%) | 2 (7.7%) | 15 (51.7%) | 2 (11.8%) |
| *ALDH2*1/2*2 or ALDH2*2/2*2* | 32 (66.7%) | 24 (92.3%)[c] | 14 (48.3%) | 15 (88.2%)[c] |

[a] Thirteen patients had both esophageal SCCs and oropharyngolaryngeal SCCs. The total number of patients is 107.
[b] 1 drink = 12 g of ethanol.
[c] $P < 0.05$ by Fisher's exact test.

terms of the OR, adjusted for the effects of several possible confounders by the use of a multiple logistic regression model. To avoid a possible bias in the 95% CI of OR attributable to the small sample size, we computed the exact CI by the use of SAS PROC LOGISTIC with EXACT statement. All analyses were done with the SAS statistical package (version 8.2; SAS Institute, Cary, NC).

## Results

Among the 107 subjects (62 ± 10 years of age), 95 were current drinkers and 12 were ex-drinkers. Among the current drinkers, 43 reported consuming more than six drinks (72 g of ethanol)/day. Current smokers numbered 72; ex-smokers, 31; never smokers, 4. The average pack-years of smoking were 47 ± 24. Comparison of the ages and drinking and smoking habits and *ALDH2* genotypes of the patients with and without cancer multiplicity associated with esophageal or oropharyngolaryngeal SCCs (Table 2) showed no differences between the two groups' ages or the drinking and smoking habits.

The *ALDH2*2/2*2* genotype was found in only one patient who had solitary tongue cancer. The *ALDH2*2* allele was more frequently present in patients who had multiple cancers associated with esophageal or oropharyngolaryngeal SCCs than in those who had solitary esophageal or oropharyngolaryngeal SCCs only (92.3% *versus* 66.7%, $P < 0.05$; and 88.2% *versus* 48.3%, $P < 0.05$, respectively). After adjustments for age and drinking and smoking habits, logistic regression analysis showed significantly increased risks for each multiplicity associated with either esophageal or oropharyngolaryngeal cancer in the presence of the *ALDH2*2* allele (ORs, 5.26 and 7.36, respectively; see Table 3).

The flushing questionnaire was completed by 99 of the 107 subjects (all current drinkers or ex-drinkers). Table 4 depicts the relationship between their *ALDH2* genotypes and their responses to the questionnaire. The *ALDH2*2* allele was found in 89.0% (65 of 73) of "current always," "former always," and "sometimes flushing" individuals, whereas the *ALDH2*1/2*1* genotype was present in 88.5% (23 of 26) of those who reported never flushing. Among the 67 patients with the *ALDH2*1/2*2* genotype, only 25.4% were classified as current always flushing, compared with 44.8% who were former always flushing and 25.4% who were sometimes flushing. When all three categories of flushing individuals (current always, former always, and sometimes) were considered to have inactive ALDH2, the questionnaire's sensitivity (the ratio of true inactive to all inactive ALDH2) and specificity (the ratio of true active to all active ALDH2) were 95.6% (65 of 68) and 74.2% (23 of 31), respectively.

## Discussion

This study is the first to strongly link inactive ALDH2 with susceptibility to multiple cancers in a sample of both esophageal and oropharyngolaryngeal cancer patients who were assumed to come from a population of ordinary drinkers. We had earlier reported similar associations between inactive ALDH2 and the risks for multiple intraesophageal (OR, 3.43) and esophageal cancers with oropharyngolaryngeal and/or stomach cancers (OR, 3.95) in Japanese male alcoholics (12, 15, 16) who had suffered loss of control over drinking and who had an average daily consumption of ~10 drinks (120 g of ethanol). In the present study, our patients comprised 95 current drinkers, 43 of whom reported consuming 6 drinks (72 g of ethanol) or more per day, and 12 ex-drinkers. Thus, we found that the association between inactive ALDH2 and multiple cancer susceptibility was not limited to alcoholics but was also the case with ordinary drinkers. This finding has very important implications for the development of strategies to prevent these cancers.

The presence of the *ALDH2*2* allele potentiates the carcinogenic effects of alcohol on the esophagus and oropharygolarynx in heavy drinkers (7, 10, 12, 13). On the other hand, because *ALDH2*2* generally serves as a strong protective factor against heavy drinking by making drinking unpleasant, the more heavily individuals drink, the less frequently they are found to carry the *ALDH2*2* allele (26–28). The *ALDH2*2* allele thus has opposing effects on carcinogenesis and drinking behavior. If both heavy drinking and *ALDH2*2* were positively associated with this cancer multiplicity, the effects of *ALDH2*2* would be underestimated unless adjustments were made for drinking behavior.

*Table 3* The risk for multiple-field cancerization in esophageal and oropharyngolaryngeal SCC patients

| | OR for multiple cancer (95% CI) | |
|---|---|---|
| | Esophageal SCC | Oropharyngolaryngeal SCC |
| Age (per 10 years) | 0.96 (0.52–1.79) | 0.97 (0.48–1.96) |
| Smoking, pack-years[a] | | |
| <41 | 1 | 1 |
| ≥41 | 1.09 (0.34–3.47) | 1.20 (0.21–7.39) |
| Current drinking, drinks/day[b] | | |
| <3 | 1 | 1 |
| 3–5.9 | 1.01 (0.15–8.26) | 2.96 (0.28–38.44) |
| ≥6 | 1.27 (0.18–10.94) | 1.21 (0.13–12.37) |
| Former drinking | 2.27 (0.21–28.06) | 1.23 (0.09–18.74) |
| *ALDH2*1/2*1* | 1 | 1 |
| *ALDH2*1/2*2* or *2*2/2*2* | 5.26 (1.08–51.06) | 7.36 (1.29–80.70) |

[a] For this analysis, pack-years were divided at the median.
[b] 1 drink = 12 g of ethanol.

*Table 4* ALDH2 genotypes in esophageal and oropharyngolaryngeal SCC patients, by facial flushing status

| Flushing status[a] | *ALDH2*2/2*2* (*n* = 1) No. | *ALDH2*1/2*2* (*n* = 67) No. | *ALDH2*1/2*1* (*n* = 31) No. |
|---|---|---|---|
| Current always flushing | 1 (100%) | 17 (25.4%) | 1 (3.2%) |
| Former always flushing | 0 (0%) | 30 (44.8%) | 4 (12.9%) |
| Sometimes flushing | 0 (0%) | 17 (25.4%) | 3 (9.7%) |
| Never flushing | 0 (0%) | 3 (4.5%) | 23 (74.2%) |

[a] Self-reported by 99 of 107 patients responding to the flushing questionnaire.

However, we found that crude ORs for *ALDH2*2* were practically unchanged after adjustment for age and drinking and smoking habits. Multiple logistic regression analyses showed no dose-response relationships between smoking and drinking and cancer multiplicity. Some previous reports concerning synchronous and metachronous multiple cancers associated with esophageal and head and neck cancers have shown positive associations between drinking and smoking habits and the risks for multiple cancers (5, 6). Small sample sizes might hamper confirmation of such dose-response relationships, but it is tempting to speculate that the role of the *ALDH2*2* allele dominates in comparison to the roles played by heavy drinking and heavy smoking in cancer multiplicity. One could also speculate that the increased proportion of multiple cancers in Japanese esophageal and oropharyngolaryngeal cancer patients is linked to the dramatic increase in the numbers of drinkers who have the *ALDH2*2* allele as well as with the rapid increase in per capita alcohol consumption in recent decades.

Regarding the sites of multiple cancers, 69.2% (18 of 26) of the cases associated with esophageal cancer and 94.1% (16 of 17) of those associated with oropharyngolaryngeal cancer occurred in the esophagus and/or the oropharyngolarynx. Among our sample of patients, as in an alcoholic population, the *ALDH2*2* allele enhanced the chances of multiple field cancerization, especially in the esophagus and the oropharyngolarynx. Epidemiological studies have consistently demonstrated that drinking alcohol and smoking are common risks for cancer at these sites (3). These phenomena are also related to the use of esophageal iodine staining in systematic screening for esophageal cancer in oropharyngolaryngeal cancer patients at the National Cancer Center. This screening has detected an extremely high (26.7%) rate of esophageal cancer (1). A recent study of esophageal iodine screening in Japanese oropharyngolaryngeal cancer patients also showed that *ALDH2*2* allele was an indicator of risk for an earlier stage of field cancerization: the presence of multiple esophageal dysplasias (29).

The stomach is another frequent site of the multiple cancers associated with esophageal cancer. Stomach cancer is one of the most common cancers in Japan, where its prevalence is near the highest in the world and where it is frequently concurrent with esophageal cancer (1). Although there is little epidemiological evidence that alcoholic beverages play a causal role in stomach cancer, the rate of detection of stomach cancer by endoscopy is higher for Japanese alcoholics than for the Japanese general population (8). Moreover, a strong association between cancer and the *ALDH2*2* allele has been observed in alcoholics with stomach cancer who also had oropharyngolaryngeal and/or esophageal cancer, but not in those with stomach cancer alone (13). We hypothesize that the pathogenesis of stomach cancer with oropharyngolaryngeal and/or esophageal cancer is associated with alcohol drinking and the *ALDH2*2* allele, and that it is distinct from other stomach cancers. Our finding that all seven stomach cancer patients with esophageal cancer had the *ALDH2*2* allele is compatible with the hypothesis.

There is sufficient evidence of carcinogenicity of acetaldehyde in experimental animals (20, 21). It is reasonable to speculate that the high prevalence of various cancers in persons with inactive ALDH2 is the consequence of repeated acetaldehyde exposures, because such individuals could not rapidly eliminate this carcinogenic compound after drinking ethanol. However, the reason for its selective influence on the upper aerodigestive tract is still open to question. This influence may be related to the rate of ethanol metabolism by topical mucosal enzymes (30, 31). High salivary acetaldehyde levels have been demonstrated after a moderate dose of alcohol in individuals with the *ALDH2*2* allele (32). Comparison of the acetaldehyde concentrations in the upper aerodigestive tract, stomach, and other organs would provide information crucial to the elucidation of this issue.

Also intriguing in this study was the reported flushing response among the cancer patients with *ALDH2*1/2*2*. In the general population, 85.7% of people with inactive ALDH2 always experience facial flushing after drinking alcohol (33). In individuals with long or heavy drinking histories, the intensity of the flushing response diminishes. Only 64.6% of males over age 50 (24) and 8.2% of alcoholic males with esophageal cancer (34) have reported currently always flushing, despite having the *ALDH2*1/2*2* genotype, suggesting the development of tolerance. For that reason, we designed our questionnaire to detect changes in flushing responses over time, by asking about both current and past flushing. In this study, our simple questionnaire yielded high sensitivity (95.6%) for detecting inactive ALDH2, although among the cancer patients with *ALDH2*1/2*2* those self-reporting as currently always flushing amounted to only 25.4%, a rate that falls between the above-mentioned rates for men over age 50 and alcoholic men with esophageal cancer. The weak and/or diminished intensity of the flushing response in cancer patients suggests the development of a tolerance to severe acetaldehydemia that has in turn enhanced these individuals' vulnerability to both heavy drinking and alcohol-related cancer. A large-scale study of interactions between drinking habits, the flushing response, and cancer susceptibility is needed. For the purpose of screening for susceptible individuals, the very high sensitivity for inactive ALDH2

is crucial for this questionnaire. However, its relatively low specificity and the small sample size hampered analyses for the association between multiple cancers and inactive ALDH2 predicted by this method. Attempting to develop screening tests for inactive ALDH2 with higher specificity is also an important task.

For ethanol oxidizing enzymes, cytochrome P-450 II E1, an ethanol inducible form of microsomal P-450 (35), and ADH2 (18) are also polymorphic. Several Japanese studies have reported no association between esophageal and oral cancers and the genetic polymorphism of P450 II E1 (9, 36, 37). The mutant *ADH2*2* allele, which is highly prevalent among East Asians, encodes a superactive subunit of ADH2 (18). The less active *ADH2*1/2*1* form of ADH2 has been consistently demonstrated to enhance the risk for esophageal cancer in East Asian drinkers (9, 12, 17, 34). Among Japanese alcoholics, the *ALDH2*1/2*2* and *ADH2*1/2*1* gene combination enhanced the risks for esophageal and oropharyngolaryngeal cancers in a multiplicative fashion (12, 34). The ADH2 effect is in part explained by its influence on alcohol flushing; *ADH2*1/2*1* diminishes the intensity of alcohol flushing (34). However, the *ALDH2* genotype, but not the *ADH2* genotype, determines individual's peak blood acetaldehyde concentrations (38), and the *ADH2* genotype was not associated with cancer multiplicity in Japanese alcoholics (12). Interactions between *ALDH2* and *ADH2* genotypes and multiple cancer susceptibility in the general population would be of interest for future studies.

To date, much of the research in this field has focused on Japanese male drinkers because of the small proportion of females, especially female heavy drinkers, and never drinkers in esophageal and oropharyngolaryngeal SCC patients. If the accumulation of acetaldehyde is one of the important causes of multiple esophageal or oropharyngolaryngeal cancer, it is reasonable to assume that drinking in females with inactive ALDH2 may enhance the risk for the multiple cancers. Analyses of risks in women and never drinkers are also the focus of ongoing research in our laboratories.

Regardless of the mechanism underlying susceptibility to cancer multiplicity, our findings have strong clinical implications. We recommend a careful search for multiple-field cancerization in the upper aerodigestive tract and stomach of the patient who is genetically at high risk because of inactive ALDH2 status, both before and after beginning treatment of the index cancer. Our brief flushing questionnaire showed high sensitivity for detecting inactive ALDH2 in cancer patients and thus may serve as a simple and useful means of identifying high-risk patients.

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