Health Risk Appraisal Models for Mass Screening of Esophageal Cancer in Japanese Men

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Abstract

Background: Because early squamous cell carcinoma (SCC) of the esophagus is detectable by endoscopic esophageal iodine staining with high accuracy and is easily treated by endoscopic mucosectomy, it is important to develop efficient methods for screening candidates for the endoscopic examination. Inactive aldehyde dehydrogenase-2 (ALDH2) is a very strong risk factor for esophageal SCC in alcohol drinkers and thus may be suitable as a screening tool.

Purpose: To assess the performance of health risk appraisal (HRA) models in screening for esophageal SCC in the Japanese male population.

Methods: Two types of HRA models were developed based on our previous case-control study, which included assessment of ALDH2 activity and selected risk factors (HRA-G and HRA-F: activities of ALDH2 assessed by genotype and questionnaire for alcohol flushing, respectively). Each individual’s risk of esophageal SCC was calculated quantitatively as a risk score. The sensitivity and specificity of the HRA models at various cutoff values of risk score was estimated by a leave-one-out cross-validation. The positive predictive value was estimated assuming the prevalence of esophageal SCC in the whole population to be 0.17% or 0.39% according to literatures.

Results: When individuals ranked in the top 10% of the HRA-F risk score was screened, the sensitivity was 57.9% and positive predictive value was 0.93% or 2.12% according to the above assumptions, respectively. The sensitivity was slightly better by the HRA-G model than by the HRA-F model.

Conclusion: The HRA models may provide an important approach to early intervention strategies to control esophageal SCC in Japanese men.

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Introduction

Because early squamous cell carcinoma (SCC) of the esophagus and oropharyngolarynx can be treated by endoscopic mucosectomy (1, 2) or endoscope-guided mucosectomy (3), it is important to develop methods to identify individuals at increased risk of cancer of the upper aerodigestive tract to provide detailed examinations by the upper aerodigestive tract endoscopy combined with esophageal iodine staining. Without using the esophageal iodine staining, more than half of intraepithelial or mucosal esophageal SCC would be missed (2, 4). A possible approach to mass screening of high-risk individuals is to classify them according to exposure to risk factors such as heavy alcohol drinking and smoking. However, the prevalence of drinkers and smokers in Japanese men is so high (e.g., 35.7% of men drink every day and 43.3% are current smokers in 2004; ref. 5) that it is not practical to conduct detailed endoscopic examinations on all of them; therefore, a more effective screening method is required.

A mutant allele encoding an inactive subunit of aldehyde dehydrogenase-2 (ALDH2*2) is prevalent (42%) in the Japanese population (6), and the ALDH2 genotype determines an individual’s blood acetaldehyde concentration (7). Acetaldehyde has been established as a carcinogen in experimental animals (8) and is suspected of playing a critical role in cancer development in humans (9). Case-control studies in Japanese (10-13) and Taiwanese (13-16) individuals and prospective studies in which esophageal iodine staining has been used in Japanese alcoholics (17-19) have consistently shown a very strong link between the risk of esophageal SCC and alcohol drinking in people possessing the ALDH2*1/*2 genotype. Alcohol drinking together with the ALDH2*1/*2 genotype has been reported to be a risk factor for multiple cancerization in the upper aerodigestive tract (13, 17, 19-21) and for oropharyngolaryngeal SCC (13, 18, 20, 22, 23). The IARC has recently concluded that substantial mechanistic evidence in humans with inactive ALDH2 indicates that acetaldehyde derived...
from the metabolism of ethanol in alcoholic beverages contributes to esophageal cancer (9). Because drinking a small amount of alcohol results in acetaldehydemia and unpleasant alcohol flushing responses in persons with inactive ALDH2, the activity of ALDH2 can be assessed by a simple questionnaire that asks about both current and past facial flushing (24, 25). This simple questionnaire about flushing as a marker of inactive ALDH2 is a highly reliable means of detecting inactive ALDH2 and predicting the risk of SCC in the upper aerodigestive tract (11, 18, 22, 25-27).

Increased mean corpuscular volume (MCV) is associated with alcohol drinking, especially drinking by inactive ALDH2 heterozygotes, and with smoking, low body mass index, and poor nutrition, all of which increase the risk of SCC in the upper aerodigestive tract (26, 27). We showed recently that MCV is a marker for drinkers who are at high risk of SCC in the upper aerodigestive tract (18, 26-28).

Based on our previous case-control study of esophageal SCC in Japanese men (12, 25), we developed simple health risk appraisal (HRA) models that predicted an individual’s risk of developing esophageal cancer based on logistic regression analyses. In addition to drinking habits, smoking habits, and diet, the HRA models included either ALDH2 genotype or the results of a simple questionnaire about alcohol flushing (26). Each individual was ranked according to his risk of esophageal SCC. Persons in the top 10% risk category for esophageal SCC, as estimated by the HRA model that included ALDH2 genotype, were selected with high sensitivity by two simple criteria, that is, the combination of moderate/heavy drinking plus “heavy smoking or alcohol flushing” and the combination of moderate/heavy drinking plus “heavy smoking or MCV ≥ 99 fl” (26). If these models are valid for the screening of high-risk individuals for esophageal SCC, a detailed examination by endoscopy of such high-risk individuals may provide an efficient method for detecting early esophageal SCC. In the present study, we assessed the performance of screening methods with our HRA models in terms of sensitivity, specificity, and positive predictive value (PPV) to identify individuals with and without esophageal SCC.

Materials and Methods

Data of Case-Control Study

Study Subjects. We previously conducted a case-control study of 234 male cases with esophageal SCC and 634 male cancer-free controls and reported the results (12). The case participants were male Japanese patients with primary esophageal SCC undergoing treatment at the National Cancer Center Hospital, National Cancer Center Hospital East, Kawasaki Municipal Hospital, or National Osaka Hospital. The cancer-free controls were men who came to two Tokyo clinics for annual health checkups, and most of them were ordinary residents or workers living in Tokyo or surrounding areas. The age-adjusted prevalences of current smokers and habitual drinkers in the controls were very similar to those in the Tokyo metropolis assessed by the National Nutrition Survey in Japan, a nationwide population-based survey using representative samples (29). Thus, the controls represented the general population of Tokyo well, at least with regard to drinking and smoking habits (12). The ethics committee of each collaborating institute reviewed and approved the proposal for this study, and each of the participants gave his informed consent.

Measurement of Risk Factors. Each participant independently completed a structured questionnaire concerning his drinking, smoking, and dietary habits; those with cancer were instructed to report on their habits before they got sick. The contents of the questionnaire and the method of calculating alcohol consumption (1 unit = 22 g, the ethanol content of one serving of sake) were described previously (12). The subjects were classified as never/rare drinkers, ex-drinkers, or current drinkers who consumed 1 to 8.9 units/wk (light drinkers), 9 to 17.9 units/wk (moderate drinkers), or ≥18 units/wk (heavy drinkers). MCV was measured during the health checkups in the

Table 1. Risks of esophageal SCC according to selected risk factors including ALDH2 genotype or alcohol flushing

| Risk factors | Estimated multivariate risks of esophageal SCC, OR* (95% confidence interval) |
|--------------|--------------------------------------------------------------------------------|
| Multivariate model including ALDH2 genotype | Alcohol drinking |
| **2*/1** | Never/rare | 0 (not calculable) |
| | Light | 1 (reference) |
| | Moderate | 5.58 (1.54-20.25) |
| | Heavy | 10.38 (2.85-37.84) |
| | Ex-drinker | 8.81 (1.53-50.76) |
| **2*/2** | Never/rare | 0.75 (0.14-4.11) |
| | Light | 5.82 (1.59-21.38) |
| | Moderate | 55.84 (15.40-202.51) |
| | Heavy | 88.88 (23.97-329.57) |
| | Ex-drinker | 50.50 (9.18-277.95) |
| **2*/2** | Never/rare | 1.44 (0.22-9.54) |
| | Light | 0 (not calculable) |
| **Strong alcoholic beverages** | Smoking | 2.36 (1.52-3.65) |
| | Green-yellow vegetables | 1.65 (1.00-2.66) |
| | Fruit | 1.73 (1.01-2.94) |
| Multivariate model including alcohol flushing | Flushing | Alcohol drinking |
| **Any** | Never/rare | 1 (reference) |
| | Light | 1.27 (0.27-5.88) |
| | Moderate | 10.12 (3.45-29.69) |
| | Heavy | 15.61 (5.19-46.91) |
| | Ex-drinker | 27.31 (5.24-142.46) |
| **Current/former** | Light | 6.69 (2.21-20.20) |
| | Moderate | 42.66 (14.17-128.42) |
| | Heavy | 72.86 (23.75-223.57) |
| | Ex-drinker | 37.00 (7.66-178.76) |
| **Strong alcoholic beverages** | Smoking | 3.59 (1.63-7.87) |
| | Green-yellow vegetables | 2.62 (1.71-4.00) |
| | Fruit | 1.65 (1.03-2.64) |
| | Fruit | 1.57 (0.94-2.62) |

* Simultaneously adjusted for all the variables (including age; not shown) in each multiple logistic regression model. These ORs were estimated by our previously reported case-control study. See refs. 12 and 25 for details.

1 Frequent versus never/sometimes (reference).

2 ≥30 versus <30 pack-years (reference).

3 Not every day versus almost every day (reference).
controls and at the time of diagnosis of esophageal SCC in the cases. The activity of ALDH2 was assessed by ALDH2 genotype and a facial flushing response to alcohol drinking. The PCR-restriction fragment length polymorphism method had been done on lymphocyte DNA samples to determine the ALDH2 genotype (12). The flushing response was assessed by two questions (25): (a) Do you have a tendency to flush in the face immediately after drinking a glass of beer (yes, no, or unknown)? (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 (yes, no, or unknown)? The designation “current flushing” was applied to individuals who answered “yes” to question (a) and “former flushing” to those who answered “no” or “unknown” to question (a) and “yes” to question (b). The remaining subjects were classified as “never flushing.” Current or former flushing individuals were assumed to have inactive ALDH2.

This approach identified inactive ALDH2 genotype with 90% sensitivity and 88% specificity in the cancer-free controls (25). Data on ALDH2 genotype were available for 234 cases and 634 controls (12); data on alcohol flushing were available for 233 cases and 610 controls (25). The distribution of ALDH2 genotypes in the control subjects was similar to that reported in other Japanese studies (6, 10, 23).

### Table 1

| Risk factors | Score (select one each for A-E) |
|--------------|---------------------------------|
| ALDH2 genotype and alcohol drinking | |
| ALDH2*1/*1 Never/rare (<1 unit/w) | -12.94 |
| | Light (1-8.9 units/w) | 0.00 |
| | Moderate (9-17.9 units/w) | 1.72 |
| | Heavy (18+ units/w) | 2.34 |
| | Ex-drinker | 2.18 |
| ALDH2*1/*2 Never/rare (<1 unit/w) | -0.29 |
| | Light (1-8.9 units/w) | 1.76 |
| | Moderate (9-17.9 units/w) | 4.02 |
| | Heavy (18+ units/w) | 4.49 |
| | Ex-drinker | 3.92 |
| ALDH2*2/*2 Never/rare (<1 unit/w) | 0.37 |
| | Light (1-8.9 units/w) | 0.00 |
| Drinks strong alcoholic beverages frequently | |
| Yes | 1.52 |
| No | 0.00 |
| Smoked 30 pack-years or more | |
| Yes | 0.86 |
| No | 0.00 |
| Eats green-yellow vegetable almost every day | |
| Yes | 0.00 |
| No | 0.49 |
| Eats fruit almost every day | |
| Yes | 0.00 |
| No | 0.54 |

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

**Predicted risk**

| Bottom 25% | 1.02 |
| 25-49% | 1.03-2.33 |
| 50-74% | 2.34-3.60 |
| 75-89% | 3.61-4.56 |
| Top 10% | 4.57+ |

### Figure 1

HRA model for esophageal cancer that includes ALDH2 genotype. The risk score is calculated as the sum of scores A to E. The higher the score, the higher the risk. For example, if an individual’s risk is ≥4.57, his risk of esophageal SCC is in the top 10% in this study population.

### HRA Models

**Scoring Each Individual’s Risk of Esophageal SCC.** Table 1 summarizes the estimated odds ratios (OR) of selected risk factors for esophageal SCC in our previously reported case-control study (12, 25). We calculated the risk of esophageal SCC for each cancer-free control subject by the previously reported method (26) based on alcohol drinking, ALDH2 genotype (or alcohol flushing), smoking, and intake of vegetables and fruit, using the formula: $RR_i = \exp[z_i - z_0/\hat{\beta}]$, where RR$_i$ is the $i$th individual’s OR [vs. the reference individual, who is a light drinker with the ALDH2*1/*1 genotype (or a never/rare drinker with any category of alcohol flushing), does not drink strong alcohol beverages frequently, smoked less than 30 pack-years, and eats vegetables and fruit every day]; $z_i$ is an observed vector of the $i$th individual’s risk factors; $z_0$ is a vector of the reference individual’s risk factors; and $\hat{\beta}$ is the vector of logistic regression coefficients estimated in our previously reported case-control study (12, 25). In other words, the $i$th individual is $RR_i$ times more likely to develop esophageal SCC than the reference individual. In actual practice, the above formula is equivalent to simply calculating the product of RRs that correspond to the individual’s risk factors. For example, computation with the estimation model that includes the ALDH2 genotype is illustrated below. When the $i$th individual is a moderate drinker with...
ALDH2*1/*2 (log OR = 4.02 (OR = 55.84); see Table 1 and Fig. 1), does not drink strong alcohol beverages frequently (log OR = 0), smoked ≥30 pack-years (log OR = 0.86), and does not eat vegetables and fruit every day (log OR = 0.49 and 0.54, respectively), his risk is calculated as the sum of these log ORs (log RRi = 4.02 + 0 + 0.86 + 0.49 + 0.54 = 5.91). Hereafter, each subject’s RRi (for the i-th individual versus the reference subject) is designated as RRind to express his risk of esophageal SCC. The subjects were classified into five risk categories based on the percentiles of the log RRind value among all controls in our previous case-control study (12, 25): bottom 25%, 25% to 49%, 50% to 74%, 75% to 89%, and top 10%.

The procedures used to make these calculations are summarized in Figs. 1 and 2. Although the calculations are relatively simple, because an electronic calculator may be required to sum the scores with two decimal places and it may be inconvenient in clinical situations or for mass-screening purposes, we further simplified the HRA model that included alcohol flushing by converting the scores to small integers (“integer score” in Fig. 2). The integer score was obtained by multiplying the original score by a constant, 2.265, and then rounding to the nearest integer, with the constant having to meet the following three conditions: (a) each integer score must be between 0 and 10, so that most people are able to sum them in their head; (b) the Spearman rank correlation coefficient between totals of the original scores and totals of the integer scores must be close to 1.0; and (c) a cutoff value that divides the subjects into the approximately top 10% and bottom 90% should be established because we intend to identify the top 10% risk individuals from the population and conduct a detailed examination of them by endoscopy with esophageal iodine staining. When 2.265 was used as the constant, it yielded a Spearman rank correlation coefficient of 0.997 and a cutoff value of 11, which selected 11.1% of the subjects.

**Cross-Validation Study.** The performance of the HRA models was assessed in terms of sensitivity (the percentage of subjects predicted to have a cancer among the cancer cases), specificity (the percentage of subjects predicted to be cancer-free among the cancer-free controls), and PPV (the percentage of patients with cancer among the selected high-risk individuals). The maximum likelihood estimates of the logistic regression model most effectively predict the data that generated them but do not perform so well when used for predictions on new data (30). Therefore, the sensitivity and specificity were estimated by the cross-validation method, which is a data-oriented method to more correctly assess the performance of a statistical model for predicting new data (30). We used the leave-one-out cross-validation method as follows:

1. Let Q be the percentage of subjects (0 < Q < 100%) to be selected as candidates for detailed examinations by endoscopy.
2. Remove one subject from the case-control data (n subjects in total) and generate a HRA model, as described above, using the remaining cases and controls (n - 1 subjects in total). Calculate RRind for each of the remaining controls and the left-out subject using this HRA model.
3. If the RRind for the left-out subject is above or equals to the (1 - Q) / 100th percentile of the RRind for the remaining controls, the left-out subject is predicted to have a cancer; otherwise to be cancer-free.
4. Repeat nos. 2 and 3 by removing each of the cases and controls n times in total.

### Figure 2.
HRA model for esophageal cancer that includes alcohol flushing. The risk score is calculated as the sum of scores A to E. The higher the score, the higher the risk. The integer score is prepared for a self-administered questionnaire in mass screening, where each participant calculates his risk score in his head.

| Risk factors                                      | Score (select one each for A-E) | Total score = A + B + C + D + E |
|--------------------------------------------------|--------------------------------|----------------------------------|
| Alcohol flushing and drinking                     | Original score | Integer score | Predicted risk | Total score | Original | Integer |
| Any flushing                                      | (<1 unit/w)    | 0.00 (8)      |                  | Bottom 25%  | 0-2      |
| Never/rare                                       |                  |                |                  | 25-49%     | 1.19-2.78 |
| Light                                            | (1-8.9 units/w) | 0.24 (1)      |                  | 50-74%     | 2.79-3.80 |
| Moderate                                         | (9-17.9 units/w)| 2.31 (5)      |                  | 75-89%     | 3.81-4.70 |
| Heavy                                            | (≥18 units/w)   | 2.75 (6)      |                  | Top 10%    | 4.71+    |
| Ex-drinker                                       |                  | 3.31 (7)      |                  | 11+        |          |
| Current/former flushing                          |                  |                |                  |            |          |
| Light                                            | (<1.8 units/w)  | 1.00 (4)      |                  |            |          |
| Moderate                                         | (1.9-17.9 units/w)| 3.75 (9)   |                  |            |          |
| Heavy                                            | (≥18 units/w)   | 4.29 (10)     |                  |            |          |
| Ex-drinker                                       |                  | 3.61 (8)      |                  |            |          |
| Drinks strong alcoholic beverages frequently      |                  |                |                  |            |          |
| Yes                                              | 1.28 (3)        |                  |                  |            |          |
| No                                               | 0.00 (0)        |                  |                  |            |          |
| Smoked 30 pack-years or more                     |                  |                |                  |            |          |
| Yes                                              | 0.96 (2)        |                  |                  |            |          |
| No                                               | 0.00 (0)        |                  |                  |            |          |
| Eats green-yellow vegetable almost every day      |                  |                |                  |            |          |
| Yes                                              | 0.00 (0)        |                  |                  |            |          |
| No                                               | 0.50 (1)        |                  |                  |            |          |
| Eats fruit almost every day                      |                  |                |                  |            |          |
| Yes                                              | 0.00 (0)        |                  |                  |            |          |
| No                                               | 0.45 (1)        |                  |                  |            |          |

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The percentage of models that correctly predict the left-out cases to have a cancer is the cross-validated sensitivity; the percentage that correctly predict the left-out controls to be cancer-free is the cross-validated specificity. We computed the receiver operating characteristic (ROC) curve for the HRA models by changing Q from 0 to 100% for calculation of cross-validated sensitivity and specificity. The area under the curve was computed via numerical integration of the ROC curve.

If PPV is extremely low, the esophagoscopy with iodine staining would not be practical in terms of cost efficiency. Therefore, we estimate PPV, which is a function of sensitivity, specificity, and prevalence of disease in a whole population (p) according to the following formula (31):

$$\text{PPV} = \frac{p \times \text{sensitivity}}{p \times \text{sensitivity} + (1 - p)(1 - \text{specificity})}$$

The data on sensitivity and specificity are available as explained above. However, data on prevalence of the esophageal cancer in the whole population are very limited, and mass screening for targeting esophageal cancer by the esophageal iodine staining technique has not been conducted for the whole population. The detection rate of esophageal cancer by endoscopy in men ages ≥40 years was 0.39% in the Research Center for Cancer Prevention and Screening Program (32), where esophageal iodine staining was applied when the mucosal surface appeared abnormal. The detection rates of stomach cancer by mass screening using endoscopy were 0.87% among 11,679 people ages ≥40 years in Niigata city in 2004 (33). Because the incidence of esophageal cancer was only 19.3% of that of stomach cancer in men ages ≥40 years and the incidence of stomach cancer was higher in men than in women in Japan in 2001 (34), the detection rate of esophageal cancer would be higher than 0.17% (0.87% × 0.193) according to these data. Thus, we assumed two different detection rates of 0.17% and 0.39% (lower and higher assumptions, respectively) for the detection rate of esophageal cancer (≥p by esophageal endoscopy with iodine staining) in the whole population.

We also calculated the sensitivity and specificity of three simple combinations of criteria for estimating the risk of cancer: moderate-to-heavy drinking plus smoking ≥30 pack-years; moderate-to-heavy drinking plus “smoking ≥30 pack-years or alcohol flushing”; and moderate/heavy drinking plus “smoking ≥30 pack-years or MCV ≥ 99 fl” (26). The sensitivity is the percentage of cases who met the criterion; the specificity is that of controls who did not meet it.

All statistical analyses were done with the SAS statistical package version 9.1 (SAS Institute).

Results

Figure 3 shows the cross-validated ROC curves of the two HRA models (HRA-G: activity of ALDH2 assessed by the genotype and HRA-F: activity of ALDH2 assessed by the flushing questionnaire) for predicting esophageal cancer. The ROC curve of HRA-F model showed that when people in the top 10% of risk scores were selected for detailed endoscopic examinations, 57.9% (sensitivity at cutoff value of 90th percentile) of cancer cases in the whole population were expected to be included in them. The HRA-G model selected cancer cases with a higher sensitivity (65.4%) at this cutoff value. When the 80th percentile was used as the cutoff value, 73.8% (HRA-F model) or 76.9% (HRA-G model) of all cancer cases were selected as candidates for detailed endoscopic examinations, mildly improving the sensitivity at the cost of a doubled false-positive rate. It should be noted that the specificity is approximately equal to the cutoff value (denoted as the percentile) by definition but could be slightly different because of ties (equal ranking) of scores (e.g., 23% of controls are above or equal to the 80th percentile by the HRA-F model). The area under the curve was slightly higher for the HRA-G model than HRA-F model (0.86 and 0.84, respectively).

The sensitivity and specificity for the simple combinations of criteria are also shown in Fig. 3: (A) moderate-to-heavy drinking plus “smoking ≥30 pack-years or alcohol flushing,” (B) moderate/heavy drinking plus “smoking ≥30 pack-years or MCV ≥ 99 fl,” and (C) moderate-to-heavy drinking plus smoking ≥30 pack-years. Criterion (C) showed relatively low sensitivity (60.1%) and false-positive rate (23.3%); criterion (A) showed relatively high sensitivity (72.5%) and false-positive rate (27.7%). All

![Figure 3. Sensitivity and specificity for screening esophageal SCC by two HRA models (HRA-G and HRA-F) and three other simple criteria (A-C).](image-url)
criteria were below the ROC curves of HRA models, indicating that these combinations of risk factors were not as useful as the HRA models.

Figure 4 shows the expected PPV among individuals selected by the HRA-F model at different cutoff values. When people in the top 10% of risk scores were selected for detailed endoscopic examinations (cutoff value = 90th percentile), the expected PPV were 0.93% and 2.12% according to the lower and higher assumptions for the prevalence in the whole population, respectively.

In the HRA-F model, the top 10% of individuals were selected by the original score of 4.71 or above, whereas 96% of them were selected by the integer scores of ≥11 (data not shown), showing that the integer score can be used instead of the original score for the mass-screening purpose.

Discussion

This study assessed the performance of screening methods for detecting individuals who have a high risk of esophageal cancer using HRA models that were developed based on our previous case-control study (12, 25). Because each individual’s risk is calculated as a quantitative score and the risks differ extraordinarily among the individuals (e.g., RR<sub>ind</sub> ranked at the bottom 25th and top 10th percentiles differ 83-fold by the HRA-G model), we can give a higher priority for detailed examination to those who have the higher scores. The sensitivity and specificity of the HRA-G model are slightly superior to those of the HRA-F model, but the low-cost is a significant advantage of the latter. When we select individuals with the top 10% risk scores of HRA-F, the sensitivity is 57.9%. This means that approximately 60% of esophageal cancer in the whole population can be detected by examining only 10% of them. Furthermore, the expected detection rate of esophageal cancer among the screened high-risk men (PPV) is 0.93% based on a lower assumption and may be more than 2% through the use of advanced diagnostic technology including esophageal endoscopy combined with iodine staining (higher assumption). If these indexes of screening are true, the application of our HRA models for the mass screening of esophageal cancer would be highly cost-efficient.

The generalizability of our estimates of sensitivity, specificity, and PPV depends on the difference in distributions of risk factors between the background population of our case-control study and the target population to which the HRA models are applied. Especially, the prevalence of screening ALDH2 and alcohol drinking would strongly affect the performance of screening using the HRA models. The magnitude of the ALDH2-associated risk depends on the extent of the association between the evaluated cancer and alcohol consumption and the proportion of alcohol drinkers with inactive ALDH2. Case-control studies in high-risk rural regions in China, where alcohol drinking plays a less important role in esophageal carcinogenesis than in Japan and Taiwan, showed moderate-to-modest positive or no associations (35-37) between inactive heterozygous ALDH2 and esophageal cancer risk. A case-control study in a Thai population, where only 18% of the controls have inactive ALDH2, also showed a marginally significant modest positive association (38). The inhibitory effect of inactive heterozygous ALDH2 on alcohol drinking is influenced by sociocultural factors; thus, only 3% of Japanese alcoholics had the inactive heterozygous ALDH2 in 1979 as opposed to 8% in 1986 and 13% in 1992 (39).

This phenomenon inversely suggests the possibility, using the HRA models, that alcohol consumption by inactive ALDH2 heterozygotes is decreased by social intervention such as public education. Thus, the HRA models that include inactive ALDH2 or alcohol flushing should be changed according to different regions and different eras in Asia. ALDH2-related susceptibility to esophageal SCC has been shown in Japanese female heavy drinkers (11). However, a much smaller proportion of women with heterozygous ALDH2 are drinkers in comparison with men, resulting in a smaller population attributable risk of esophageal SCC for alcohol drinking plus heterozygous ALDH2 in women than in men (11, 12). Therefore, we intended to apply our HRA models for screening esophageal cancer in Japanese male populations. The proportion of people selected by our cutoff value for the top 10% risk may be smaller than 10% in a population where the prevalence of drinkers is small or vice versa. However, the importance of screening for esophageal cancer in such a low-risk population would be relatively small. The age-adjusted death rates from esophageal cancer differ considerably among the 47 prefectures in Japan (40) and are strongly correlated with annual per capita consumption of alcoholic beverages in each prefecture (ref. 41; Spearman’s rank correlation coefficient = 0.68; P < 0.0001). Further studies are needed to clarify the geographical difference.
in the distribution of HRA risk score among Japanese male populations.

From a cost-efficiency point of view, the HRA-F to detect esophageal cancer in a mass screening has the advantage that it is available almost at no cost and deliverable not only at the clinic but also via mass media, Internet, and other sources. For the screened top 10% high-risk individuals, the cost of endoscopic esophageal iodine staining is 12,000 Japanese yen (JPY; 1 US$ \approx 105-108 JPY in June 2008) per person. Thus, the cost to identify one case of esophageal cancer is roughly estimated, by dividing 12,000 JPY by the PPV, to be 570,000 to 1,290,000 JPY (higher and lower assumptions, respectively), which is less expensive than that of gastric cancer by endoscopic screening (1,608,000 JPY) and photofluorography (3,290,000 JPY) in a Japanese population (33). As for the HRA-G, the expected PPV (2.40% and 1.06% for higher and lower assumptions, respectively, with the cutoff value of the top 10%) is slightly better; thus, the estimated cost of endoscopic examination to identify one case of esophageal cancer is somewhat smaller (500,000-1,130,000 JPY, respectively) than that of HRA-F. However, a large initial cost would be required for genotyping of ALDH2 for all individuals in the target population. The additional cost to identify one case of esophageal cancer is estimated as the unit cost of genotyping divided by the detection rate of cancer among all subjects, and this may far exceed the cost of endoscopic examination. However, it should be emphasized that genotyping is needed only once in a lifetime and the data are available repeatedly; and the unit cost would be largely discounted when a huge number of samples is analyzed.

On the other hand, we have no data to analyze the effectiveness of mass screening to decrease mortality from esophageal cancer because there has been no large-scale screening of esophageal cancer conducted in Japan. When an asymptomatic high-risk population was screened by a combination of endoscopy and esophageal iodine staining, 76% of the esophageal cancer detected did not invade the submucosa (4). Such early esophageal cancer can be safely treated by endoscopic mucosal resection, and the patients are generally hospitalized for only a week or less (1) with relatively low medical costs. Notably, the cause-specific survival rates 5 years after endoscopic mucosal resection for esophageal cancer not invading the submucosa have been reported to be 95% to 98% (1, 42), whereas the 5 year-survival rate of esophageal cancer based on data from a population-based cancer registry was reported to be 25% among seven prefectures of Japan (43). Therefore, it is expected that implementation of screening for esophageal cancer could improve the prognosis and decrease the mortality substantially. However, the actual effectiveness, considering the costs, must be analyzed based on the results of mass screening in a large population in the future.

A parallel study on oral and pharyngeal SCC conducted in men who came to the same clinics and hospitals showed that hypopharyngeal SCC and esophageal SCC shared several common risk factors including ALDH2 genotype, alcohol flushing, drinking habits, smoking habits, and diet (12, 22, 25). Figure 5 shows the ROC curves for detecting hypopharyngeal SCC by the HRA models for esophageal SCC. The sensitivity was 62.7% when the top 10% was screened by the HRA-F model and the areas under the curve are very similar to those of esophageal SCC. Although the HRA models were designed based on the results of a case-control study of esophageal SCC, they can be applied to hypopharyngeal SCC as well.

The combination of alcohol flushing and MCV with the traditional risk factors of drinking and smoking improved the predictive power of esophageal and pharyngeal SCC in comparison with the combination of drinking and smoking alone, which was in good agreement with our previous study (26). However, a substantially greater proportion (28.2% and 30.6%) of subjects met the two criteria, which is a disadvantage when using these criteria to select candidates for cancer screening.

One of the limitations of our study may be that the HRA models are not based on a prospective cohort study, but a case-control study that could have some biases in principle. However, it is unlikely that the potential biases affect the results notably because the estimated RRs are exceptionally strong. Another limitation is that we could not assess the risk of age. Because the incidence rate of esophageal cancer increases above the age of 50 years (34) and the majority of esophageal cancer patients in our case-control data is older than 50 years (12, 25), it may be appropriate that our HRA models are used for mass screening in those age groups. The age distributions of cases and controls did not match substantially. However, it is unlikely that the estimated RRs are exceptionally strong. Another limitation is that we could not assess the risk of age. Because the incidence rate of esophageal cancer increases above the age of 50 years (34) and the majority of esophageal cancer patients in our case-control data is older than 50 years (12, 25), it may be appropriate that our HRA models are used for mass screening in those age groups. The age distributions of cases and controls did not match substantially.
adjustment for age might have unexpected effects. To address this issue, we repeated the cross-validation study for men ages 70 to 79 years and confirmed that, at the cutoff value of top the 10%, the sensitivity was similar to (60.0% and 57.5% for HRA-G and HRA-F, respectively) and the specificity was somewhat better than (93.3% and 96.7%, respectively) those of other age groups, showing a good performance of our HRA models even in this old age group. However, the sample sizes in these groups are so small (40 cases and 30 controls) that further investigations are needed for the elderly ages ≥70 years.

Although alcohol flushing is a marker of inactive ALDH2, the sensitivity and specificity of the flushing questionnaire for identifying inactive ALDH2 in a Japanese male population was 90% and 88%, respectively (25). The advantage of the model that included alcohol flushing over the model that included ALDH2 genotype is that it facilitates risk estimation and can be easily applied to both public education and screening. Our HRA functions, which are very easily calculated on a simple sheet of paper (Figs. 1 and 2), may not only provide a means of screening the high-risk individuals but also help persuade those people to change their drinking habits, smoking habits, and diet. Cessation of drinking and smoking has been shown to reduce the risk of cancer of the upper aerodigestive tract (44, 45). Early cancer of the esophagus (1, 2) and pharynx (3) can be easily treated by endoscopic mucosectomy or endoscope-guided mucosectomy, and the HRA models we used may provide an important approach to early intervention strategies to control these high-mortality cancers in Japanese men. Further study is needed to confirm the effectiveness of this new approach in large Japanese populations.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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