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Abstract

Purpose: To assess the performance of our health risk appraisal (HRA) models for screening individuals at high risk of esophageal/pharyngeal squamous cell carcinoma (EPSCC).

Methods: Based on the results of our previous case-control study, we invented HRA models that enable screening for EPSCC cases in Japanese men with high sensitivity and specificity based on either their aldehyde dehydrogenase-2 genotype (HRA-G model) or alcohol flushing (HRA-F model) and drinking, smoking, and dietary habits. Follow-up endoscopy combined with esophageal iodine staining (median follow-up period: 5.0 years) was done on 404 Japanese men (50-78 years) who were registered as cancer-free controls in the previous study.

Results: The follow-up endoscopy resulted in a diagnosis of 6 esophageal SCC (Tis in 5 and T1 in 1), 1 hypopharyngeal SCC (T2), and 1 oropharyngeal SCC (T2). Seven and 6 of the 8 EPSCC cases were in the top 10% risk group at baseline according to the HRA-G and HRA-F models, respectively. The EPSCC detection rates per 100 person-years in the top 10% risk groups by the HRA-G and HRA-F models were 4.38 (95% confidence interval, 1.76-9.01) and 3.48 (95% confidence interval, 1.28-7.58), respectively. Their age-adjusted relative risk was 95.1- and 26.3-fold, respectively (P < 0.0001), higher than in the bottom 90% risk groups.

Conclusions: The high detection rates for EPSCC in the top 10% risk group of this preliminary follow-up study were in good agreement with those predicted by the HRA models and thus encouraged the screening based on our HRA models in larger populations of Japanese men.

Introduction

Recent technical improvements in endoscopes and growing understanding of the endoscopic findings of early squamous cell carcinoma (SCC) in the esophagus (1, 2) and pharynx (3) have made it possible to detect esophageal/pharyngeal SCC (EPSCC) early. Treatment of early esophageal SCC by endoscopic mucosectomy has become a widespread practice in Japan and has succeeded in improving the prognosis of this high-mortality cancer (2, 4, 5), and early pharyngeal SCC can also be treated by endoscope-guided mucosectomy (6). Therefore, it is important to identify individuals at increased risk of EPSCC and offer them the opportunity to undergo detailed examination by 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 (1, 7).

A mutant allele encoding an inactive subunit of aldehyde dehydrogenase-2 (ALDH2*2) is prevalent in East Asian populations (e.g., prevalence of the ALDH2*2 allele is 24% in a Japanese population; ref. 8) and drinking a small amount of alcohol results in severe acetaldehydemia and unpleasant alcohol flushing responses in individuals with inactive ALDH2 (9). Acetaldehyde is an established carcinogen in experimental animals (10) and is suspected to play a critical role in cancer development in humans (11). Case-control studies among Japanese (12-16) and Taiwanese (13, 17, 18)
and prospective studies among Japanese alcoholics (19, 20) have consistently shown a markedly increased risk of EPSCC in drinkers possessing ALDH2*1/*2. Our previous case-control studies confirmed that alcohol drinking especially in individuals with inactive ALDH2, tobacco smoking, a preference for drinking concentrated alcoholic beverages straight, and less intake of green and yellow vegetables increased the risk of EPSCC in Japanese men (12, 16, 21). Based on the data we obtained in that study, simple health risk appraisal (HRA) models were developed to be able to quantitatively assess individual risk of developing EPSCC in the form of a risk score (22). A cross-validation study, which used a simulation-based approach to assess the performance of a statistical model, predicted that 60% of the EPSCC in the entire population could be detected by examining only people with the top 10% risk scores of the HRA models (sensitivity = 60% and specificity = 90%; ref. 22). Furthermore, the detection rate of esophageal SCC in people with the top 10% risk score (positive predictive value) was expected to be >2%. If it is possible to achieve these performances levels in an actual mass screening, a very efficient approach to early detection of EPSCC in Japanese men will have been achieved.

The present study was a 7-year follow-up study of cancer-free men who were the controls in our previous case-control study and was conducted to confirm that the good performance of HRA models predicted by the cross-validation study was also achieved in an actual follow-up study, where the subjects were examined repeatedly by using a combination of upper aerodigestive tract endoscopy and esophageal iodine staining.

Materials and Methods

Study Population. 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 cancer-free controls were men who came to two Tokyo clinics for annual health checkups between September 2000 and December 2001, and most of them were ordinary residents or workers living in Tokyo or surrounding areas. The cancer-free controls who had been recruited in one of the two clinics and diagnosed as cancer-free by upper gastrointestinal endoscopy when they registered to participate in the previous study were sent annual letters of invitation to be screened by endoscopy. As of April 2007, 404 (81.3%) of the 497 eligible men ages 50 to 78 years had undergone a combination of follow-up endoscopic screening and esophageal iodine staining at least once, and they were enrolled in the present study. The Ethics Committee of the Kurihama Alcoholism Center reviewed and approved the proposal for this study, and each of the participants gave his informed consent.

Endoscopic Screening. Endoscopy was done with an Olympus Q240 or Q240Z panendoscope (Olympus Optical) by one of the authors (Y.K.), who is an expert in the field of upper gastrointestinal endoscopy. The endoscope was inserted into the pharynx, and it was carefully examined while removing secretions by
suction. After advancing the endoscope beyond the upper esophageal sphincter, the esophageal mucosa was flushed with 40 mL water through the biopsy port. Conventional endoscopic inspection was done from the esophagus down to the duodenum, and the esophagus was stained with then 10 mL of 1.5% iodine solution and inspected again. Mucosal biopsy specimens were collected from lesions that remain distinctly unstained by iodine, if their greatest diameter was ≥5 mm. At the end of the screening procedure, the esophageal mucosa was rinsed with 20 mL of 2.5% sodium thiosulfate solution, and the gastric contents were removed by suction.

Measurement of Risk Factors. At the time of baseline registration for the previous study, each participant was asked to fill out a simple questionnaire that asked the questions concerning alcohol flushing response, drinking habits, smoking habits, and diet (12). Alcohol flushing is a surrogate marker of inactive ALDH2 and the sensitivity and specificity of the flushing questionnaire for identifying inactive ALDH2 in a Japanese male population were 90% and 88%, respectively (21). The PCR-RFLP method has been done on lymphocyte DNA samples to determine their ALDH2 genotype (rs671) of all participants in the previous case-control study (12).

We calculated the HRA score to assess the risk of esophageal SCC in each subject at the time of registration based on alcohol drinking, either ALDH2 genotype (HRA-G model) or alcohol flushing (HRA-F model), smoking, and intake of vegetables and fruit according to the previously reported method (22). The subjects were classified into five risk categories according to their HRA scores: bottom 25%, 25% to 49%, 50% to 74%, 75% to 89%, and top 10%. The procedures used to make these calculations are summarized in Fig. 1 (HRA-G) and Fig. 2 (HRA-F). The HRA score was calculated as the sum of the scores (A-E), which were logarithms of the multivariate odds ratio of each factor estimated in the previous case-control study (12, 21). We further simplified the HRA-F model by converting the scores to small integers (“integer score” in Fig. 2), so that the categorization of the risk group was approximately the same as the categorization based on the original scores (22).

Statistical Analyses. The cancer detection rates during the follow-up period were calculated by the person-year method, with “person-year” defined as time from the baseline examination to either cancer detection or the most recent follow-up examination, whichever came first. The 95% confidence interval (95% CI) of the detection rate was estimated based on a Poisson distribution. The relationships between the HRA score at baseline and results of subsequent endoscopic screening are expressed as relative risk of cancer detection rate adjusted for decade of age by the Mantel-Haenszel method. All statistical analyses were done with the SAS statistical package (version 9.1; SAS Institute).

Results

The mean follow-up period was 4.4 years [median (25th and 75th percentiles), 5.0 (3.3, 5.6) years; range, 0.1-6.7 years]. There were no significant differences between the distribution of the HRA scores of the subjects who underwent the follow-up screening and those who did not (P > 0.4, Fisher’s exact test; data not shown). Follow-up endoscopy resulted in a diagnosis of primary esophageal SCC in 6 subjects, SCC in 5 (Tis), and SCC in 6 subjects, SCC in 5 (T1a), and SCC...
plus basolaid carcinoma in 1 (T1) and primary SCC of the hypopharynx (T2) and oropharynx (T3) in 1 subject each. At baseline, all 8 subjects who were diagnosed with EPSCC at follow-up were moderate/heavy drinkers (>200 g ethanol/wk) and heterozygotes for inactive ALDH2, and 7 of them reported current/former alcohol flushing. Seven of the subjects with EPSCC had smoked ≥30 pack-years, 5 did not eat green-yellow vegetables almost every day, and 7 did not eat fruit almost every day.

Table 1 shows the detection rate of cancer during the follow-up period according to risk category based on the HRA models. Five of the 6 esophageal SCC patients and 7 of the 8 EPSCC patients had been classified in the top 10% risk category based on the HRA-G model, and 4 of the esophageal SCC patients and 6 of the EPSCC patients had been classified in the top 10% risk category based on the HRA-F model. The detection rate of esophageal SCC per 100 person-years (95% CI) was 3.13 (1.01-7.29) and 2.32 (0.63-5.94) in the top 10% risk group based on HRA-G and HRA-F models, respectively, and that for EPSCC was 4.38 (1.76-9.01) and 3.48 (1.28-7.58), respectively. The age-adjusted relative risk in the top 10% risk group was much larger than in the bottom 90% risk group and the difference was highly significant (P < 0.0001) in both models. The results based on the HRA-F model obtained with integer scores were very similar to the results obtained with the original scores (data not shown).

**Discussion**

We invented HRA models that allow prediction of ~60% of patients with EPSCC while referring only the top 10% of risk category of Japanese high-risk men for endoscopic screening (22). The present study investigated whether the HRA models would perform well in terms of actual endoscopic screening for cancer during a 7-year follow-up of Japanese men. The results showed that 7 (88%) of the 8 EPSCCs developed in individuals ranked in the top 10% risk category according to the HRA-G model and 6 (75%) developed in individuals ranked in the top 10% risk category according to the HRA-F model, showing better performance in comparison with the proportions (= sensitivity) predicted by the cross-validation method (65.4% and 57.9%, respectively; ref. 22). It was noteworthy that the esophageal cancers detected were in the very early stage (Tis cancer in 5 and T1 cancer in 1). An esophageal cancer detection rate by endoscopy in men ages ≥40 years was reported to be 0.39% in the Research Center for Cancer Prevention and Screening of the National Cancer Center (23), where esophageal iodine staining was applied when the mucosal surface did not appear normal. We estimated the esophageal cancer detection rates in the top 10% category according to the HRA-G model and HRA-F model to be 2.40% and 2.12%, respectively, based on the overall detection rate (0.39%) in the Research Center for Cancer Prevention and Screening (22), and those rates were in good agreement with the results of the present study (3.13 and 2.32, respectively, per 100 person-years). The high skill level of the endoscopists and the use of esophageal iodine staining probably contributed to the high rates of esophageal cancer detection in the Research Center for Cancer Prevention and Screening and the present study, because more than half of the cases of intraepithelial or mucosal SCC in the esophagus would have been missed without esophageal iodine staining (1, 7). The precise incidence of esophageal Tis SCC in the Japanese general population and its natural course are unknown, and they will be topics of future research.

Our follow-up study had several potential limitations. The intervals between the follow-up screening and the baseline screening that confirmed freedom from cancer...
were short, and the very small number of cancer cases may have limited the assessment of the relationship between the HRA scores and actual rate of cancer development. Although the follow-up was incomplete (81.3%), there were no significant differential follow-up biases. The performance of HRA models could depend on the difference in distributions of risk factors between the background population of the present study and the target population to which the HRA models are applied (22). Further investigation of the relationship in a large, long-term prospective study in different populations with a high follow-up rate is clearly warranted.

Our HRA-F model enables many people to identify their own risk of EPSCC very easily, and public awareness campaigns using the HRA-F model will help persuade high-risk persons to undergo endoscopic screening and enable detection of EPSCC early or enable them to change their lifestyle to prevent ESCC. Although the number of cancers detected was small, the very good performance of the HRA models in this preliminary follow-up study provided evidence supporting the validity of the HRA risk scores for selecting individuals at high-risk of EPSCC and encouraged the use of these new models for screening in larger populations of Japanese men. Further study is needed to confirm the effectiveness of this approach in large Japanese populations.

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

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References

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