Abstract. Background/Aim: Recently, mounting evidence has shown that caspase-8 (CASP8) rs3834129 (-652, 6N insertion/deletion) polymorphism may serve as a genetic biomarker for personal risk of various cancer types. The contribution of CASP8 rs3834129 polymorphism has been investigated in several oral cancer populations, but not in Taiwan. This study investigated the role of CASP8 rs3834129 polymorphism on oral risk in Taiwan. Materials and Methods: CASP8 rs3834129 polymorphic genotypes were determined and their associations with oral cancer risk were investigated among 788 patients with oral cancer and 956 age- and gender-matched healthy controls via polymerase chain reaction-restrictive fragment length polymorphism (PCR-RFLP) methodology. In addition, the interaction of CASP8 rs3834129 genotype with personal behavior and clinicopathological features were also examined. Results: The frequencies of II, ID and DD genotypes for CASP8 rs3834129 were 57.5, 36.5 and 6.0% in the patient group and 54.0, 39.0 and 7.0% in the healthy control group, respectively (p for trend=0.3052), genotypes were not significantly differentially distributed between the two groups. The comparisons in allelic frequency distribution also supported the findings that the D variant allele may not serve as a determinant of risk for oral cancer. There was no interaction of CASP8 rs3834129 genotype with age, gender, smoking, alcohol or betel quid consumption in regard to oral cancer risk. Conclusion: Our results indicate that the caspase-8 genotype does not appear to play a direct role in personal susceptibility to oral cancer in Taiwan.

Oral cancer is the eighth most commonly diagnosed cancer among men in the world, and about twice more prevalent than among women in the world (1). In Taiwan, the incidence and mortality of oral cancer has occupied the fourth and fifth places among the common cancer types for many years (2), and its high incidence has been proposed to be closely associated with the combative effects of smoking, alcoholism and, betel quid chewing in addition to genetic factors (3-6). However, the definitive genomic etiology of oral cancer remains largely unknown. In Taiwan, although several useful biomarkers for early detection of oral cancer have been revealed (7-13), the mechanisms underlying them are largely unknown and practical genomic markers for clinical use are still in urgent need. Noticeably, Taiwan has over of the highest densities worldwide of patients with oral cancer.

Apoptosis is a bio-essential mechanism for altering the morphology, and controlling the death rate of a stable population (14). In the literature, mounting evidence has shown loss of homeostasis of the apoptosis pathway to be associated with the development of oral cancer (15), and...
genomic polymorphisms of caspase-8 (CASP8), one of the most important components of this family of proteins in extrinsic apoptosis signaling (16, 17), may serve as a biomarker for oral cancer.

Among the polymorphic sites of CASP8, rs3834129 (-652, 6N ins/del) polymorphism, a six-nucleotide insertion (I)/deletion (D) variant, has been functionally identified to lead to down-regulation of the mRNA of CASP8 (18). Caspase-8 single nucleotide polymorphisms are reported to be genomic markers for the prediction of the personal risk for several types of cancers such as that of the digestive tract (19, 20), breast (21-23), prostate (24), lung (25) and bladder (26), and neuroblastoma (27). Little is known about the role of CASP8 polymorphisms in oral cancer.

In 2017, one epidemiological study on a South Indian oral cancer population reported no association between CASP8 rs3834129 polymorphism and oral cancer risk (28), a finding which has not yet been validated in other populations. Thus, in the current study, we aimed to determine the genotype of CASP8 rs3834129 polymorphism, evaluate its association with oral cancer risk, and examine the joint effects of CASP8 rs3834129 genotype with lifestyle factors in a representative Taiwanese population.

Materials and Methods

**Collected population.** The protocols in collecting participants for the current study were approved by the Institutional Review Board of the China Medical University Hospital (DMR101-IRB1-306), while written-informed consent was obtained from all the participants. In total, 788 patients diagnosed with oral cancer were recruited in this study. All participants voluntarily joined, fully understood the purpose and aims of the study, willingly completed a self-administered questionnaire and provided 5 ml of their peripheral blood. The questionnaire contents helped the translational scientists to fully understand the cancer history and frequency of alcohol consumption, areca chewing and smoking habits of the participants. The alcohol consumption, areca chewing and smoking habits for each participant were evaluated and classified as categorical variables. Information on these personal behaviors were further evaluated by defining that occurring more than twice a week for years as ‘ever’. A total of 956 non-cancer healthy individuals were selected by matching for age and gender after initial random sampling from the Health Examination Cohort of the hospital, and excluding those with any history of cancer themselves or for their first-order relatives. The male versus female ratio was 76% to 24% in the case and control groups, while the average ages of the case and control groups were 55.8 (SD=9.9) and 56.6 (SD=8.7) years, respectively. The information of selected characteristics for all the participants is concisely summarized in Table I.

**Genotyping conditions for CASP8 rs3834129.** The genomic DNA for each participant was extracted from their peripheral blood leukocytes with the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan, ROC), and stored long-term at −80°C, subsequently 100-fold diluted and aliquoted for genotyping as a working stock at −20°C as previously published (6, 29). The genotyping methodology for CASP8 rs3834129 regarding the designing of the primer pairs and the selection of restriction enzyme were as follows. In brief, the polymerase chain reaction (PCR) cycling conditions were: one cycle at 94°C for 5 min; 35 cycles of 94°C for 30 s; 59°C for 30 s and 72°C for 30 s; with a final extension at 72°C for 10 min. The sequences of forward and reverse primers for CASP8 rs3834129 were 5’-ACTCTGCATGCCAGGAGCTA-3’ and 5’-CTGGGG AAGCCCTGACTGTAT-3’, respectively. After PCR amplification by Light Cycler (BioRad, Hercules, CA, USA), the PCR products were subject to restriction endonuclease digestion with *Pvu* II (New England Biolabs, Beverly, MA, USA) according to the manufacturer’s instructions. The digestive products were then separated using 3% agarose gel electrophoresis and visualized with ethidium bromide staining under UVC irradiation. All the genotypic processing was repeated by at least two well-trained researchers independently and blindly, and the results were 100% concordant with each other, while the success rates of PCR-restrictive fragment length polymorphism (RFLP) were 100%. To confirm the results of PCR-RFLP, the genotypes of 5% of the samples chosen randomly from the overall pool (control and patient groups) were subjected to PCR direct sequencing (Genomics BioSci & Tech Co.). The rates of concordance between direct sequencing and PCR-RFLP methods were 100% for each of the samples double-checked.

**Statistical analyzing methodology.** Student’s *t*-test was specifically applied for the comparison of continuous variables (age) between the case and control groups. Pearson’s chi-square test was applied to compare the distribution of the CASP8 genotypes among the subgroups. The associations between CASP8 genotypes and oral cancer risk were estimated by calculating the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) via the logistic regression analysis. Finally, any difference between the two groups at *p*<0.05 was identified as being statistically significant.

| Characteristic                  | Controls (n=956) | Cases (n=788) | *p*-Value |
|--------------------------------|-----------------|---------------|-----------|
| Age (years)                    | 56.6±8.7        | 55.8±9.9      | 0.7951    |
| Gender, n (%)                  |                 |               |           |
| Male                           | 727 (76.0%)     | 599 (76.0%)   | >0.99     |
| Female                         | 229 (24.0%)     | 189 (24.0%)   |           |
| Personal habit, n (%)          |                 |               |           |
| Cigarette smoking              | 667 (69.8%)     | 595 (75.5%)   | 0.0084    |
| Alcohol drinking               | 641 (67.1%)     | 560 (71.1%)   | 0.0773    |
| Betel quid chewing             | 506 (52.9%)     | 661 (83.9%)   | <0.0001   |
| Primary tumor site, n (%)      |                 |               |           |
| Tongue                         | 325 (41.2%)     |               |           |
| Buccal mucosa                  | 294 (37.3%)     |               |           |
| Mouth floor                    | 30 (3.8%)       |               |           |
| Retromolar trigone             | 26 (3.3%)       |               |           |
| Alveolar ridge                 | 18 (2.3%)       |               |           |
| Palate                         | 18 (2.3%)       |               |           |
| Lip                            | 39 (4.9%)       |               |           |
| Other                          | 38 (4.9%)       |               |           |

SD: Standard deviation; *a*Based on Student’s *t*-test; *b*Based on chi-square test. Significant *p*-values (*p*<0.05) are shown in bold.
The data on age, gender, personal habits and primary tumor sites for the 788 patients with oral cancer and 956 non-cancer controls are summarized in Table I. Since we applied the frequency matching approach during choosing the non-cancer healthy participants, there was no difference in the frequency distribution of age and gender between the oral cancer case and control groups (Table I). Among the investigated population, it was found that betel quid chewers and smokers were significantly more frequent in the oral cancer patient group than in the control group (both p<0.05), indicating that these two lifestyle factors are potential predictors of oral cancer risk for Taiwanese (Table I). From the clinical viewpoint, tongue (41.2%) and buccal mucosa (37.3%) were found to be the two most common tumor sites for primary oral cancer (Table I).

### Results

**Comparison of basic characteristics between the oral cancer and the healthy control groups.** The data on age, gender, personal habits and primary tumor sites for the 788 patients with oral cancer and 956 non-cancer controls are summarized in Table I. Since we applied the frequency matching approach during choosing the non-cancer healthy participants, there was no difference in the frequency distribution of age and gender between the oral cancer case and control groups (Table I). Among the investigated population, it was found that betel quid chewers and smokers were significantly more frequent in the oral cancer patient group than in the control group (both p<0.05), indicating that these two lifestyle factors are potential predictors of oral cancer risk for Taiwanese (Table I). From the clinical viewpoint, tongue (41.2%) and buccal mucosa (37.3%) were found to be the two most common tumor sites for primary oral cancer (Table I).

**Association of CASP8 genotypes and Taiwan oral cancer risk.** The distributions of the CASP8 rs3834129 genotypes among the non-cancer healthy controls and the patients with oral cancer are presented and analyzed in Table II. The genotypes of CASP8 rs3834129 were not differentially distributed among the investigated cases and the controls (p for trend=0.3052) (Table II). CASP8 rs3834129 heterozygous and homozygous variant ID and DD genotype was not associated with altered oral cancer risk compared with the wild-type II genotype (p=0.2057 and 0.2633, respectively). In addition, in the dominant model, there was no significant
The genotypes (Table IV). No significant effect of genotype was interested in evaluating the joint effects of the statistical results were still non-significant for ID and DD Taiwanese. Firstly, among non-smokers, those with ID and genotypes with these risky personal behaviors among the DD genotypes at 24.2% (n=382 out of 1,576) in the oral cancer patient group, Weinberg equilibrium (slightly but non-significantly lower than that of 26.5% (n=507 frequency distributions for rs3834129 in the control group fit well with the Hardy–Weinberg equilibrium (pHWE=0.9709).

In order to validate the results in Table II, analysis of allelic frequency distributions for CASP8 rs3834129 was also conducted and the results are presented in Table III. Supporting the idea that genotype of CASP8 rs3834129 was not associated with oral cancer risk, the frequency of variant allele D was 24.2% (n=382 out of 1,576) in the oral cancer patient group, slightly but non-significantly lower than that of 26.5% (n=507 out of 1,912) in the control group (p=0.1244) (Table III).

From the epidemiological viewpoint, smoking, alcoholism and betel quid chewing habits are well-known risk factors for oral cancer in Taiwan. Therefore, we were extremely interested in evaluating the joint effects of CASP8 rs3834129 genotypes with these risky personal behaviors among the Taiwanese. Firstly, among non-smokers, those with ID and DD genotypes at CASP8 rs3834129 were at 0.89- and 0.78-fold odds of developing oral cancer (p=0.5514 and 0.5200) (Table IV). After adjusting for confounding factors including age, gender alcohol drinking and betel quid chewing habit, the statistical results were still non-significant for ID and DD genotypes (Table IV). No significant effect of genotype was found among the non-smokers (Table IV). Secondly, among the subgroups of non-alcohol and alcohol drinkers, genotypes of CASP8 rs3834129 were not significantly associated with risk of having oral cancer (Table V). Among the subgroups of non-betel quid chewers and betel quid chewers CASP8 rs3834129 genotype similarly was not associated with risk of having oral cancer either (Table VI).

**Discussion**

The CASP8 gene encodes a cysteine-aspartic acid protease 8 which activates caspase-3 in the apoptosis signaling cascade (30). CASP8 plays an initiator of both extrinsic and intrinsic apoptotic pathways after being activated by Fas cell surface death receptor (FAS) and Fas-associated death domain (FADD), the Fas-interacting protein (31, 32). Activated CASP8 may work alone or cooperate with another apoptosis initiator caspase-10, contributing to the subsequent activation of the downstream executioner caspases, such as caspase-3 to complete the apoptotic process (33). Among the single nucleotide polymorphisms of CASP8, rs3834129 is the most commonly examined and has attracted much more interest of genomic scientists. In 2007, Sun and his colleagues firstly screened a panel of cancers to investigate the associations of CASP8 rs3834129 with each type (34), showing that the

### Table V. Odds ratios for caspase-8 rs3834129 genotype and oral cancer after stratification by alcohol drinking habit.

| Genotype | Non-drinkers, n | OR (95% CI) | aOR (95% CI) | p-Value | Drinkers, n | OR (95% CI) | aOR (95% CI) | p-Value |
|----------|-----------------|-------------|--------------|---------|-------------|-------------|--------------|---------|
| II       | 166             | 1.00 (ref)  | 1.00 (ref)   |         | 350         | 1.00 (ref)  | 1.00 (ref)   |         |
| ID       | 131             | 0.79 (0.55-1.13) | 0.85 (0.63-1.38) | 0.1903  | 242         | 0.93 (0.73-1.18) | 0.92 (0.58-1.25) | 0.5420 |
| DD       | 18              | 0.98 (0.47-2.04) | 0.99 (0.54-1.79) | 0.9529  | 49          | 0.73 (0.46-1.17) | 0.85 (0.52-1.13) | 0.1933 |

**p**-trend 0.4153 0.4038

I: Insertion; D: deletion; OR: odds ratio; aOR: adjusted OR; CI: confidence interval. *Multivariate logistic regression analysis. bAdjusted for age, gender and smoking habit. *Chi-square without Yates’ correction or Fisher’s exact test (when n<5).

### Table VI. Odds ratios for caspase-8 rs3834129 genotype and oral cancer after stratification by betel quid chewing habit.

| Genotype | Non-chewers, n | OR (95% CI) | aOR (95% CI) | p-Value | Chewers, n | OR (95% CI) | aOR (95% CI) | p-Value |
|----------|-----------------|-------------|--------------|---------|-------------|-------------|--------------|---------|
| II       | 240             | 1.00 (ref)  | 1.00 (ref)   |         | 276         | 1.00 (ref)  | 1.00 (ref)   |         |
| ID       | 178             | 0.85 (0.56-1.29) | 0.91 (0.63-1.26) | 0.4432  | 195         | 0.90 (0.71-1.15) | 0.93 (0.73-1.21) | 0.4044 |
| DD       | 32              | 0.82 (0.36-1.86) | 0.88 (0.53-1.47) | 0.6379  | 35          | 0.81 (0.50-1.31) | 0.89 (0.51-1.27) | 0.3890 |

**p**-trend 0.7075 0.5507

I: Insertion; D: deletion; OR: odds ratio; aOR: adjusted OR; CI: confidence interval. *Multivariate logistic regression analysis. bAdjusted for age, gender and smoking habit. *Chi-square without Yates’ correction or Fisher’s exact test (when n<5).
deletion (D) allele at CASP8 rs3834129 was associated with a reduced susceptibility to several types of cancer, such as lung, colorectal, esophageal, breast, cervical and gastric. During the period of 2008 to 2017, CASP8 rs3834129 genotype was found to contribute to personal susceptibility to melanoma (35), brain tumor (26), breast cancer (23) and kidney cancer (36). As for the contribution of CASP8 rs3834129 genotypes to oral cancer, del allele of CASP8 rs3834129 was reported to be protective in oral squamous carcinoma (37).

Mechanistically, the deletion (D) genotype at CASP8 rs3834129 was reported to destroy a stimulatory protein 1 binding element in the promoter regulatory region, reducing CASP8 transcription and eventually reducing apoptosis of T-lymphocytes (34).

In the current study, we firstly found that the genotype of CASP8 rs3834129 was not significantly associated with oral cancer risk in a representative Taiwanese population with 788 patients with oral cancer and 956 healthy controls (Tables II and III). The highlight finding is consistent with a previous one from a study performed on a South Indian population (28) with negative association results. In addition, after adjusting for the confounding factors, there was still no association between the CASP8 rs3834129 genotype with oral cancer risk (data not shown). Furthermore, we analyzed the interaction of CASP8 rs3834129 genotypes and three risk lifestyle behaviors for Taiwanese, smoking, alcohol drinking, and betel quid chewing. The results indicated that there was no interaction between CASP8 rs3834129 genotype and smoking, alcohol drinking, or betel quid chewing in determining the personal susceptibility to oral cancer (Tables IV-VI). We also examined the correlation between genotypes of CASP8 rs3834129 and clinicopathological features of investigated patients with oral cancer in Taiwan.

In conclusion, the study provided a preliminary findings showing that CASP8 rs3834129 was not associated with altered risk for oral cancer in a Taiwanese population. Additionally, in the stratified analyses, we found no alteration of risk according to behaviors believed to contribute to the etiology of oral carcinogenesis. Moreover, the CASP8 rs3834129 variant genotype was not found to be a predictor for metastasis or recurrence.

**Conflicts of Interest**

All the Authors declare no conflict of interest.

**Authors’ Contributions**

Research design: Shih LC, Tsai CW and Sun KT; patient and questionnaire summarizing: Shih LC and Shen TC; experiment performance: Hsu HM, Wang YC and Chang WS; statistical analysis: Tsai YT and Lin ML; article writing: Gong CL, Tsai CW and Bau DT; reviewing and revising: Bau DT, Chang WS and Tsai CW.

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