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Multiple logistic regression analysis of risk factors for carcinogenesis of oral submucous fibrosis in mainland China

S. Zhou[1], F. Guo[1], L. Li[3], Y. Zhou[3], Y. Lei[2], Y. Hu[1], H. Su[1], X. Chen[1], P. Yin[1], X. Jian[1]

[1]Department of Oral and Maxillofacial Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, P.R.China; [2]Department of Orthodontics, Xiangya Hospital, Central South University, Changsha, Hunan, P.R.China; [3]Cancer Research Institute, Xiangya School of Medicine, Central South University, Changsha, Hunan, P.R.China

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Abstract. Oral submucous fibrosis (OSF), a chronic progressive disorder, is regarded as the premalignant lesion of oral squamous cell carcinoma (OSCC). Its distribution is associated with chewing betel quid (BQ). The objective of the present study was to investigate risk factors for the carcinogenesis of OSF in mainland China. A case-control study was performed in 42 patients with OSCC that originated from OSF and 40 OSF controls. Epidemiological data and information related to risk factors were collected using a short structured questionnaire. Odd ratios (OR) and 95% confidence intervals (CI) were derived from logistic regression analysis. In multivariate analysis, only age, duration of BQ chewing, duration of cigarette smoking, and OSF accompanied by oral leukoplakia or oral lichen planus were associated with significantly increased risk for the malignant transformation of OSF. These findings contribute to current knowledge on the prevention of carcinogenesis of OSF in mainland China.

Keywords: OSF; carcinogenesis; risk factor; logistic regression analysis.

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Oral squamous cell carcinoma (OSCC) is the eighth most common cancer worldwide, according to the World Oral Health Report 2003 released by the World Health Organization (WHO); it is also the most frequent malignant tumor of the oral cavity (90% of all tumors). In Asia, cancer of the oral cavity ranks among the three most common types of cancer, the standardized incidence rate of oral cancer per 100,000 population ranges from 0.7 in China to 4.6 in Thailand and 12.6 in India. Despite many therapeutic strategies, the ratio of 5-year survival in patients with OSCC is low. Unnecessary treatment of oral disease can influence the quality of life, therefore it is important to clarify the pathophysiology of OSCC in the early stage.

Oral carcinogenesis is a complex, multi-step process that results from multiple environmental factors and genetic susceptibility. Most OSCC arise in clinical premalignant lesions[17], including

oral leukoplakias (OLK)[16], oral lichen planus (OLP) and oral submucous fibrosis (OSF). OSF is a chronic progressive disorder characterized by a juxtaepithelial inflammatory reaction followed by fibroelastic change in the lamina propria and associated epithelial atrophy, resulting in restricted mouth opening[12]. It is predominantly seen in South and Southeast Asia, including India, Bangladesh, Pakistan and Taiwan. On the Chinese mainland, OSF is common in the Hunan and Hainan provinces. Chewing betel quid (BQ), containing areca nut or slaked lime, is the most important risk factor for OSF[21].

The precancerous nature of OSF was first described in 1956, subsequently the five criteria that prove that OSF is precancerous were identified[4,14]. The malignant transformation rate of OSF is 7–13% for populations in India and Taiwan[10,11,13]. In 1985, Jian et al. reported two cases of OSF in mainland China (from Hunan)[7]. With the development of society and an increase in the number of people chewing BQ, the incidence of OSF has increased. In an epidemiological study on oral cancer and precancerous lesions in mainland China, the malignant transformation rate of OSF was 1–2% over a 10-year period, and it is expected to rise[2,8]. The pathogenesis of the malignant transformation of OSF is thought to be multifactorial; the ingredients and chewing method of BQ vary in different areas. Studying the risk factors for the carcinogenesis of OSF in mainland China might contribute to knowledge about the prevention of this disease. The aim of this study was to determine the risk factors for the malignant transformation of OSF in mainland China.

Methods

Subjects

A case-control study was conducted in mainland China. A total of 42 patients with OSCC that had progressed from OSF were identified in the surgical pathology archives (from 1990 to 2007); they were recruited to the study when they entered the Department of Oral and Maxillofacial Surgery at Xiangya Hospital in Southern China. Forty patients with OSF, newly diagnosed without OSCC, admitted to the same hospital for surgical procedures from 2002 to 2007 were also recruited. Patients were excluded from the study if they had other chronic diseases, psychiatric disease or had undergone radiotherapy and chemotherapy. The diagnosis of OSF, OSCC, OLK and OLP was based on histological examination of haematoxylin-eosin stained tissue sections using the WHO criteria[15].

Analysis

The following 13 items obtained from medical records by history and questionnaire were analysed as risk factors: sex; age; occupation; educational level; oral health; diet; duration of BQ chewing; duration of alcohol drinking; duration of cigarette smoking; presence of OLK or OLP; bad prosthesis or sharp cusp; OSF pathological stage; and mouth opening.

For each factor, 2–5 categories were established. Age was classified into groups of under 40 years, 40–49 years, 50–59 years and over 60 years. Occupation included farmer, worker, staff and others. Because the educational level sometimes influenced oral habits, the education levels were divided into under or equal to high school and up to or over undergraduate. General, bad and worse were used to judge the oral health of the patients. Insipid and acrid were used to differentiate the diets. The period of chewing BQ was classified as under 5 years (short duration), 5–9 years (moderate duration) and over 10 years (long duration). The period of alcohol drinking was classified as no drinking, 1–19 years and over 20 years (addiction). The period of cigarette smoking was classified as no smoking, 1–9 years (short duration), 10–19 years (moderate duration) and over 20 years (long duration). The presence or absence of OLK or OLP was included in the diagnosis of OSF and OSCC. Whether there was a bad prosthesis or sharp cusp was noted. OSF pathological stage was divided to early stage, moderately advanced stage and advanced stage according to WHO criteria. The prominent clinical characteristic of OSF is restricted mouth opening, which was classified into over 2.5 cm, 2–2.4 cm, 1–1.9 cm and under 1 cm.

Statistical analysis

Univariate logistic regression analysis was performed to calculate the odds ratio (OR) and to examine the predictive effect of each factor on the risk for malignant transformation of OSF. The 13 potential risk factors for OSCC originating from OSF patients were compared with those of the OSF patients using Fisher's exact test, with the software package SPSS 13.0 (SPSS Inc., Chicago, Ill., USA); $P < 0.05$ was considered statistically significantly. Significant risk factors were entered into a forward selection multivariate logistic regression analysis.

The involvement of the various factors in the development of OSF carcinogenesis was analysed using multiple logistic regression analysis with the SPSS statistical software package. The logistic model is a multivariate analysis model by which the OR (a good approximate value for the relative risk) of prognostic factors is calculated by logit transformation of the probability of the development of the end point. Using this model, the degree of involvement of each factor in the malignant transformation of OSF could be estimated. When the 95% confidence interval (CI) of the relative risk of a given factor does not include 1, the value is significant ($P < 0.05$). To adjust for the effects of each factor, these factors were simultaneously incorporated into the model.

Results

In all, 42 patients with OSCC originating from OSF and 40 patients with OSF were interviewed. They included 42 men, aged 33–65 years (mean 45 years); 26 men had carcinoma of the tongue, 12 had carcinoma of the buccal mucosa, 4 had carcinoma of the gingiva. The 40 control patients included 38 men and 2 women, aged 16–52 years (mean 38 years). There were no significant differences between cases and controls with regard to sex, occupation, educational level, oral health, diet, duration of alcohol drinking, bad prosthesis or sharp cusp, and OSF pathological stage.

The results of univariate logistic regression analysis are shown in Table 1. Compared with the age group under 40 years, the age groups 40–49 (OR 14.17, 95% CI 4.02–49.90) and 50–59 (OR 8.50, 95% CI 1.51–47.96) were at higher risk for OSF carcinogenesis. The malignant transformation of OSF risk was significantly greater in those chewing BQ for over 10 years (OR 9.78, 95% CI 1.98–48.26), and those smoking cigarettes for 10–19 years (OR 3.00, 95% CI 0.44–20.44) or over 20 years (OR 12.00, 95% CI 1.62–88.71). Patients with OSF associated with OLK or OLP exhibited a significant association with OSCC; mouth opening was also related to the carcinogenesis of OSF.

On multivariate analysis, mouth opening was excluded from the risk factors in the carcinogenesis of OSF, even if the mouth opening exhibited a significant association on univariate analysis (Table 2). The final model indicated that older age (OR 12.59, 95% CI 2.85–55.52, $P = 0.001$), duration of BQ chewing (OR 10.15, 95% CI 2.72–37.79, $P = 0.008$),