Environmental heavy metal as a potential risk factor for the progression of oral potentially malignant disorders in central Taiwan

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ABSTRACT

Objective: Oral cancer (OC) is a leading cause of death from cancer in men between the ages of 25 and 44 years in Taiwan. The overall 5-year survival rates for the four OC stages (I–IV) in Taiwan are approximately 70%, 30%, 20%, and 10%, respectively, indicating the importance of the early diagnosis of oral potentially malignant disorders (OPMDs). Previous studies indicated an association between the OC incidence and certain environmental heavy metal concentrations. If these associations do exist for OC, they may also be observed for OPMD. The purpose of this study is to explore the association between the development of OPMD to OC and environmental heavy metals. Oral submucous fibrosis (OSF) and oral leukoplakia (OL) are two major types of OPMD in Taiwan.
Materials and methods: A retrospective cohort study was conducted by Changhua Christian Hospital, the sole medical center in Changhua County, where 2725 male adult patients diagnosed with either OSF or OL between 2000 and 2014 were recruited. Data were analyzed by Cox regression and adjusted for smoking and betel-quid chewing.
Results and discussion: OPMD patients who resided in areas with high nickel concentrations (polluted levels) exhibited hazard ratios of 1.8–2 for OC relative to those who lived in areas with low nickel levels ($P < 0.01$). Meanwhile, smokers with OPMDs had a hazard ratio of 2.8–2.9 relative to non-smokers. Betel-quid chewers had a 2.2–2.3 hazard ratio relative to non-chewers. Smoking, betel-quid chewing, and environmental nickel exposure are associated with an increased risk of OC development in OPMD patients. This study provides valuable findings on the environmental effects of heavy metals on human health. Enhanced surveillance of the condition of OPMD patients who have been exposed to high nickel concentrations may be crucial for OC prevention.

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1. Introduction

Oral cancer (OC) has been a rapidly increasing malignancy in Taiwan in the past decade [1]. The disease is also the leading cause of death from cancer in men between the ages of 25 and 44 years [2]. The affliction of numerous young patients with this malignancy has inflicted severe losses on society. The oral cancers we refer to herein are classified by the International Classification of Diseases, Ninth Revision (ICD-9-CM) as 140 (lip); 141 (tongue); 143 (gum); 144 (floor of the mouth); 145.0 (buccal mucosa); 145.2, 145.3, and 145.5 (palate); and 145.1, 145.4, 145.8, and 145.9 (other unspecified parts of the mouth). In Taiwan, the tongue and buccal mucosa are the primary locations of 29.34% and 26.31% of cancers, respectively [23].

A study in 1999 by Chen et al. [4] demonstrated that the overall 5- and 10-year survival rates for OC patients after surgery were approximately 45% and <10%, respectively, in southern Taiwan. Moreover, their group found that the overall 5-year survival rates for the four stages of cancer (I–IV) were approximately 70%, 30%, 20%, and 10%, respectively. These facts clearly indicate that early diagnosis of OC is a decisive factor for a good prognosis.

OC is known to develop from premalignant lesions, which can be detected by visual examination. Currently, the strategy for these oral potentially malignant disorders (OPMD) is regular and close monitoring [5]. Oral leukoplakia (OL) and oral submucous fibrosis

(OSF) are the most frequent types of OPMD in Taiwan. We had [5] reported the increasing age-standardized incidence rate for OL and OSF in 2000 and 2009, with overall rates of 549.43 and 625.61 per 100,000 person-years, respectively, for males. A study based on a Chinese population reported that patients with OSF (odds ratio [OR] = 24.2, confidence interval [CI] = 7.39–79.5) or OL (OR = 4.05, CI = 2.44–6.71) had a higher risk of developing head-and-neck cancer than the general public [6].

Several studies [6–8] indicated that among OPMD patients, habitual cigarette smoking, betel-quid chewing (BQC), and alcohol drinking increase the risk of OC. Some studies [8–10] further showed significant dose-response effects of BQC or cigarette smoking on the risk of OC. On the other hand, a study [11] found that these risk factors were not significantly associated with OPMDs in southern Taiwan.

Heavy metals have been established as risk factors in many cancer types; however, fewer epidemiologic studies have linked heavy-metal ingestion to human OC. A study [12] in Germany found that metal dust containing chromium and nickel increased the risk of OC in machine workers. Occupational exposure to chromium (VI) compounds may increase the risk of oral squamous cell cancer [13]. In animal studies of the National Toxicology Program by the U.S. National Institutes of Health, researchers found that OC could be induced in rats by chronic exposure to chromium (VI) [14]. As for the effects on human health, a study in Taiwan unveiled a significant spatial correlation between the nickel concentration in farm soil and the OC incidence in townships [15].

Since the 1970′s, Changhua County has become a major cluster of electroplating factories in Taiwan. Ranking only 15th among the 19 counties in the area, this county once contained over 60% of Taiwan's electroplating factories [16]. Most of these factories are of small size and lack the ability to process their own waste; therefore, a considerable amount of their wastewater containing nickel and chromium was directly discharged into the surrounding soil [17]. Studies [16,17] show that the distribution of nickel and chromium concentration in the soil is spatially correlated to the location of electroplating factories; consequently, Changhua has the highest nickel and chromium concentrations in farm soil of all the counties in Taiwan [18].

Moreover, a study [2] found that OC patients who resided in the more highly industrialized parts of Changhua presented with younger ages at diagnosis and poorer long-term prognosis of OC. A case-control study [19] of blood samples from patients who resided in Changhua who were tested for metal concentrations by inductively coupled plasma mass spectrometry found that the patients with OC had significantly higher levels of nickel and chromium than the other subjects tested.

Several studies [15,19,20] also found that certain environmental heavy metals, such as nickel and chromium, could affect the progression and incidence of OC in Taiwan. Many types of industrial plants, such as electroplating, textile, and metal-surface treatment plants, discharge wastewater, releasing large amounts of heavy metals into irrigation systems or rivers [2,16,21,22]. Several studies [1,19,23] showed the association of the exceptionally high incidence of OC in Changhua County with the area's higher environmental heavy metal concentrations compared with those of other places in Taiwan.

If environmental heavy metal levels are associated with OC incidence, then they may also be associated with the development of OPMD to OC. To our knowledge, no study has investigated such an association. This study aims to use data from Changhua Christian Hospital to investigate the environmental risk factors for the development of OPMD to OC using time-to-event analysis.

2. Materials and methods

2.1. Data

We conducted a retrospective cohort study using medical records archived from Changhua Christian Hospital, which is the sole medical center in Changhua and has been the primary referral and treatment center for OPMD and OC in the past decades. OL and OSF are the most frequent types of OPMD in Taiwan. Among other types of OPMD, oral lichen planus is relatively rare, and the diagnosis of verrucous hyperplasia is likely confounded by the co-existence of other oral diseases. Therefore, we only considered OL and OSF in this study, and the medical records of 2921 adult patients (age ≥ 20) who lived in Changhua County and had been diagnosed with OL and OSF during 2000 and 2014 were retrieved retrospectively. During the diagnosis, each patient was asked about habitual daily BQC and smoking. To comply with the law of private data protection, each patient's address was recorded only as the alley without the plate number.

In our previous study on 254 OC patients [25], we had found that women comprised only 6% (15/254) of the OC cases in Changhua. Among male patients, 90.0% were betel-quid chewers and 91.6% were smokers, whereas among females, the prevalence rates were only 6.7% and 13.3% respectively. Similarly, among the 2921 OPMD patients in this study, the proportions of men and women were 93.3% (2725) and 6.7% (196), respectively. The BQC and smoking rates of male patients were 60% and 47.5%, respectively, much higher than those of female patients (12.8% and 8.2%, respectively). The environmental factors in the etiology of OC may be quite different between men and women; therefore, a separate analysis is necessary. Considering the sample size and power required for survival analysis, this study focused on men only. Because the site, size, and type of oral leukoplakia were not considered in this paper, by focusing on male OMPD and OC, we could obtain a homogeneous sample.

All the OPMD diagnoses were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, 528.6 and 528.8). The medical records of each OPMD or OC case were double checked by one of the authors, who is an oral surgeon at Changhua Christian Hospital. The date of OPMD diagnosis was used as the baseline date for each patient.

Starting from the 1980′s, the Environmental Protection Administration in Taiwan conducted a series of surveys on the soil levels of the following metals: arsenic, cadmium, chromium, copper, mercury, nickel, lead, and zinc. Soil data in this study were derived from a progressive, nationwide survey on measuring the concentration in topsoil (0–15 cm) of the eight heavy metals, obtained from the Environmental Protection Administration in Taiwan from 1983 to 1990. The first phase of the soil survey, conducted from 1983 to 1986, used a grid cell size of 1600 ha as a sampling unit. The 100-ha sampling unit size was used in the second phase, conducted from 1987 to 1990. The concentrations of cadmium, chromium, copper, nickel, lead, and zinc in the soil were measured by the 0.1 M HCl extraction method, while those of arsenic and mercury were obtained through the aqua regia method. Among the 19 counties in Taiwan, Changhua County has the highest concentration of nickel and chromium in the soil [19]. Environmental Protection Administration classified soil concentrations of metals into three main levels as follows: within environmental background values, possibly polluted, and heavily polluted. We pooled the last two levels into a single "polluted" category, which we compared with the "background value" in our analysis. Since 1990, the government has enhanced law enforcement monitoring of metal pollution from factories. We consider the concentration of the heavy metals in soil to have been stable for