

efficiency of oral cancer screening is the most urgent event here.

Methods: The data was collected from the special clinic for betel quid chewing related diseases in National Taiwan University Hospital, which was established in December 3, 2000. Descriptive statistic was used to analyze those data.

Results: From 2004 to August 2009, 6213 person in time were recruited. The annual number of person in time increased by year proceeding. There are 102 diseases listed, the top-five diseases are leukoplakia (45.77%), oral malignant diseases (9.32%), lichen planus (7.26%), other disturbances of oral epithelium (7.11%) and glossitis (5.6%). Most of them related to betel quid chewing. Among leukoplakia, there are 302 persons, 19 persons (6.29%) developed to have oral malignant diseases during treatment.

Conclusion: Special clinic for betel quid chewing related diseases supply the good and convenient platform for persons chewing betel quid to get early diagnosis and treatment, who had the potential malignant disorders and oral malignant diseases. It also gave the opportunity for persons with the potential malignant disorder to find the malignant transformation of their disorder early. All improve the efficiency of oral cancer screening.

SY12-05

Chemical Carcinogenesis of Betel Quid in Taiwan

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Betel quid (BQ) chewing was the main etiologic factor of oral submucous fibrosis (OSF) and oral cancer in Taiwan, India and many other countries. In the multi-step chemical carcinogenesis, BQ ingredients such as arecoline, arecaidine, safrole etc. are found to be the potential carcinogens due to their cytotoxicity, mutagenicity and genotoxicity. In addition, the production of reactive oxygen species (ROS) and areca nut-specific nitrosamines during BQ chewing may also contribute to the diseased processes. All these toxic species may involve in the initiation, promotion and progression of oral cancer by induction of gene mutation, chromosomal aberration, deregulation of cell cycle control, alteration of gene expression as well as affecting the cellular signal transduction. BQ components, such as areca nut extract, arecoline, arecaidine, catechin and copper, may also affect the collagen phagocytosis, metalloproteinases (MMPs), tissue inhibitor metalloproteinases (TIMPs), plasminogen activator inhibitor (PAI-I) and lysyl oxidase expression, collagen turnover, proliferation and the contraction of buccal mucosa fibroblasts as well as the induction of tissue inflammation, leading to occurrence of OSF. These results indicate that BQ chewing is an important etiologic factor of oral cancer and OSF. Chemical components in the BQ and their metabolic products are

possible carcinogenic and fibrotic factors.

Understanding the mechanisms responsible for toxicity of BQ ingredients may highlight our future prevention and treatment of BQ-chewing related oral mucosal diseases

SY12-06

Effects of Betel Quid Component on the Hamster Urinary Metabolome of Cigarette Containing Carcinogen,

4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone in Hamster

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Objective: The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a documented human carcinogen. We have previously shown that safrole, a major betel quid component, induced hamster hepatic CYP2As activity, which modulated NNK metabolism as evidenced by reduced urinary

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) formation. This study evaluated the synergist potential of safrole on NNK metabolism by metabolomic approach.

Methods: Male hamsters received a single administration of safrole (1 mg/kg) or an equal volume of corn oil (vehicle control) by oral gavage nine days prior to buccal painting of NNK (1 mg/kg). Urinary metabolomic profiles were determined by liquid chromatography/quadrupole time-of-flight mass spectrometry (LC/QTOF-MS) in 24-h urine after NNK treatment. The acquired LC-MS data were extracted with the Agilent MassHunter Qualitative software. Multivariate data analysis was performed with GeneSpring MS software. Finally, the concentration of selected compounds in urine was calculated using HPLC triple quadrupole mass (MS/MS) spectrometry. **Results:** NNAL, NNAL-glucuronide, NNAL-N-oxide, NNK-N-oxide, 4-(3-pyridyl)-4-hydroxybutanoic acid (HBA) and 4-(3-pyridyl)-4-hydroxybutanoic acid (OBA) were identified, together with a number of unidentified compounds. The results revealed the increased formation of NNK-N-oxide and NNAL-N-oxide in safrole/NNK group, and this reflected the increased activity of pyridine N-oxidation of NNK and NNAL. The underlying mechanism and the meaning of this pathway remain elusive and warrant further study. Safrole pretreatment also enhanced the urinary HBA and OBA formation, which indicated the metabolic activation of NNK.

The ratios of HBA/total NNAL and OBA/total NNAL represent the activation indices of NNK, and their values in safrole-pretreated and control groups were 4.06 vs 2.74 and 5.04 vs. 2.94, respectively. On the other hands,

the detoxification index of NNK, ratio of NNAL-glucuronides/free NNAL, was significantly decreased in safrole-pretreated group ($p=0.024$). Conclusion: By using Q-TOF and MS/MS spectrometry, we have demonstrated safrole modulated the activation of NNK in vivo.

SY12-07

Mechanisms of Metastasis in Betel Quit (BQ)-associated Oral Squamous Cell Carcinomas

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Betel Quit (BQ)-associated oral squamous cell carcinoma (OSCC) is, in principle, a deadly oral malignancy among all head & neck cancers, but also features unique clinical characteristics with etiology that signifies its special biological & epidemiological manifestations in southern Taiwan. We addressed to investigate the unique histo-pathological and potential mechanisms of BQ-associated OSCC in human vs. animal models via the genomics and shotgun proteomics. Herein, the discussion will be focused to reveal the underlying cellular and molecular interactions associated metabolic pathways that concur during BQ-related metastatic spread locally and systemically.

SY12-08

Reduction or Block Carcinogenesis of Betel Related Oral Submucous Fibrosis and Oral Cancer

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Objective: The previous findings of toxicogenomics affirmed us with new direction in studying the pathogenesis and prevention of betel quid/areca nut-induced oral precancerous lesions and oral cancer. Here, we undertake chemopreventive research program to find out whether we can control the disease occurrence by blocking or reducing the carcinogenic effects from ready-to-use clinical drugs.

Methods: The microarray, pathway analysis, and qRT-PCR were performed to identify susceptibility genes and novel mechanisms accounting for betel quid/areca nut-induced pathogenesis. Case-control study further ascertained the candidate genes and its risk genotype in the development of betel-related oral cancer. Moreover, approaches of toxicogenomics (areca nut) and pharmacogenomics (selective COX-2 inhibitors) on oral cell lines and animal model were utilized to recognize the significance of susceptibility genes, and further to investigate preventive effects of COX-2 inhibitors on the early areca nut-induced oral pathogenesis.

Results: Our findings suggested 12 susceptibility genes related to xenobiotic metabolism (COX-2), DNA repair, inflammatory and stress response (COX-2), and

transforming growth factor-beta signaling family. These genes may serve as potential biomarkers for betel quid/areca nut-induced damage in chewers. Further, we also showed that COX-2 promoter -1195G>A genotype has an additive interaction with betel chewing habit ($aOR=79.4$) in risk of oral cancer, and the inflammatory response of A/A genotype can be highly induced by areca nut than A/G and G/G genotype. This finding indicates the important role of COX-2 on betel-related oral cancer in Taiwan. Moreover, in chemoprevention studies, two-way cluster analysis from gene expression profiling shows that areca nut-induced damage could be recovered in a suitable dosage of a selective COX-2 inhibitor.

Conclusion: Early detection and chemoprevention are crucial strategies for reducing or blocking carcinogenesis in betel-related oral lesions. Based on our knowledge, the selective COX-2 inhibitor in chemoprevention might be useful for reducing the occurrence of betel-related oral cancer.

SY12-09

New Perspectives in the pathophysiology of Oral Cancer

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(More detail will be presented during the talk)

Symposium 13- Social Determinants of Health II

SY13-01

Social Gradient of Health in Japan; Why and How Education and Income Matter to Health

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Social gradient of health attracts social and political concerns in many countries including Japan. Education and income have long been regarded as major indicators of one's socio-economic positions in the societal hierarchy. Recent research including ours, however, pointed out that simple measurement of socio-economic position through education and/or income lacks theoretical foundation to explain the mechanism of health gradient across social strata. Education may reflect one's skills and knowledge for self-care, while it may be confounded by economic and cultural affluence of one's parents. Income may reflect the degree of access to health-promoting material resources and time, while it may also bring prestige, power, and the degree of social inclusion. Many studies found that income and education distinctively and variously relate to health behaviors, physical and mental health status across genders, age cohorts, and regions, suggesting that the influence of income and education is heterogeneous and unspecified. A recently conducted cross-sectional