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An Overview of the Detection and Screening of Oral Cancer and Precancer

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Abstract

Oral cancer is a fatal disease, which accounts for the 5th highest incidence of malignancy of male and the 7th in general population in Taiwan. The relative high prevalence of oral cancer in Taiwan is mainly because a 2.5 million high-risk group of population with smoking as well as betel nut chewing exist. Unfortunately, the new cases being found in medical center often present with a TNM stage III or IV level leading to a low 5-year survival. Therefore, it is generally accepted that prevention and screening of oral cancer at early stages or premalignant levels for the high-risk group of population are equally important to treatment. In this review article, we describe the nature of oral cancer and highlight the importance as well as various conventional and novel methods of screening of this disease.

Key words: Oral cancer, Screening, Prevention, Tumor Marker, Cytology, Betel nut.

Introduction

Oral cancer is the fifth most common cancer in the world, accounting for 412,000 new cases and 262,000 deaths annually in 1985, four-fifths of which occurred in the developing regions. Epidemiological difference exists in South Asia where oral cancer ranks first among all types of cancers in male patients and third in female patients.[1,2] Oral cancer is associated with chronic irritating factors such as tobacco, smoking, alcohol, and BQ use. While cigarette smoking and alcohol drinking are

the major risk factors in western countries, betel quid use and smoking are major factors in the causation of oral cancer in south, Southeast Asia and Taiwan.[1,2,3] About 2.5 million people are betel quid users in Taiwan. Unfortunately, a higher rate of incidence in oral cancer and its mortality have been found to have correlation with the increasing prevalence rate of betel chewing in this area. Betel chewing in Asia is generally accepted as a social custom or behavior for more than a few hundred years. According to an epidemiological study by Ko *et al* in Taiwan, the incidence of OSCC in BQ users and smokers is more than 100 times higher than the general population.[3,4] Abundant of studies had been dedicated to clarify the roles of ingredients in BQ related carcinogenesis. It is generally agreed that BQ may potentially damage the oral mucosa to induce genotoxicity or non-genotoxic effects, which may further be related to the initiation, promotion and progression of oral cancer. Basically, various ingredients of BQ including areca nuts, nitroso-derivatives, arecoline, safrole, lime and so on have been studied and correlatd to carcinogenic, co-carcinogenic effects and tumor promotion. Up till now, more studies are necessary to clarify the roles of each ingredient in BQ related carcinogenesis.[3,5-10]

Importance of early treatment

Not only oral cancer, betel quid associated diseases in the oral cavity such as mucositis, submucous fibrosis, severe tooth attrition, and periodontitis have long been a tough and challenging work in the general health care. About 50% or more of oral cancer patients were found to have their tumors ranking as stage III or stage IV at their first visit to the medical center in Taiwan. Unfortunately, the overall 5-year survival rate of these patients is poor despite recent advances in surgery, radiotherapy and chemotherapy.[4] We would give an example to highlight the importance of early treatment of oral cancer. A 50-year-old patient at his first visit to our department presented with a tumor growth measuring 4x5 cm at his right buccal mucosa-gingivae area and cervical lymph adenopathy. An oral squamous cell carcinoma T4N1M0 stage IV was diagnosed by pathological proof after incisional biopsy. The patient received a Commando operation with partial mandibulectomy leaving a huge transbuccal defect immediately reconstructed with a radial forearm osteocutaneous free flap. The patient received a 24-hour long surgery, followed by a week of intensive medical care. The final pathological report confirmed the previous tentative diagnosis. Afterwards, a combination treatment with concurrent chemotherapy and radiotherapy was thus given. Later on, he suffered severe hair loss, a radio-burned facial skin with dermatitis and intraoral mucositis with multiple areas of ulcer. Unfortunately, the patient was diagnosed with distant lung metastasis 2 years after surgery. Through consultation, chemotherapy and radiotherapy were still given as palliative treatment to control the metastasis of oral cancer. Two months later, the patient was deceased for failure of treatment. The whole expenses for his medical care estimated a total of 2 million

NT. Not surprisingly, the cost of the medical care for the treatment of a stage III or stage IV oral cancer patient was far more than those for treating a stage I or II oral cancer patient. According the retrospective study at the primary oral squamous cell carcinoma from an analysis of 703 cases in southern Taiwan by Chen et al, the 5-year survival in the patients of advanced stages was far less than those of the early stages [4]. This result again strongly suggests the importance of early diagnosis and treatment of oral cancer.

Screening the high-risk population

Yet oral cancer can be cured if treated early enough. Oral cancer is one among the few human cancers with a vast potential for prevention. Being lack of previously reliable epidemiological data on the survey of oral cancer prevention in Taiwan, so far, the value and potential of prevention and screening is on the large based on the fact that oral cavity is an organ with visual examination or access of ease. Programs for detecting oral cancer have been supported by our government for years. To cope with this, funding has been distributed to several directions including general health auxiliaries in the public first-line health care institute, dentists and ENT doctors in the medical center.[3,4] However, the long-term effect still remained not to be seen. Previous reports revealed that 90% of male oral cancer patients were both betel quid chewers and smokers. It is undoubtedly that this high-risk group accounting for 1/10 population in Taiwan should be screened with priority. Meanwhile, a follow-up system has recently been established to recall and monitor the cancer patients and patients with precancer lesions treated in the hospital.[11-14]

Premalignant lesions predisposing oral cancer

Attentions should specifically be paid to the premalignant lesions.[11-14] Although the potential for malignancy of the erythroplakia has been reported a lot higher than that of the leukoplakia, leukoplakias are among the most common seen premalignant oral lesions. Some are idiopathic and others are related to habits such as tobacco, alcohol or BQ use. About 80% leukoplakias are benign with no evidence of dysplasia, and no tendency to malignancy, but clearly biopsy is indicated to define the remaining 10-20% that are either dysplastic or already invasive carcinomas.[12] Unfortunately, there is currently no histological or other means able to reliably predict which leukoplakias are indeed potentially malignant. Overall the rate of malignant transformation of leukoplakias is about 3-6% over 10 years but higher rates have been reported. Medical management of leukoplakia includes reducing or quitting those habits relating to risk factors, increasing the intake of fruit and vegetables in the diet, and possibly the use of active agents[13]. Retinoids, carotenoids and topical cytotoxic agents inducing apoptosis show promise, and newer therapies are on the horizon.[13, 15-17]

Roles of health care workers

Health care workers need to clearly

understand their roles in cancer screening. It is sometimes argued that oral cancer screening is not necessary because routine dental examinations should include a full oral mucosa examination. However, apart from the fact that more than 50% of the over 45-year-old population do not yearly attend a dentist, there is evidence that many cases are missed, even by dental practitioners.[14,18] This is probably because early lesions are not specifically looked for or may appear to be innocuous and are ignored. Thus, other profession or specialty may also need to be included in the screening program. Screening for oral cancer is a simple, non-invasive procedure, which can easily be integrated into the comprehensive assessment of older patients who account for the major part of the oral cancer patients. Further, geriatricians might feel comfortable performing an oral cancer screening examination.[13,14,18-20] Since 5-year survival rates are more than four times greater in individuals with localized lesions than in those with distant metastases, the detection of early oral cancer can make a significant contribution.[21] The aged persons at risk for oral cancer visit their dentist far less frequently than they see their physician.[20] The primary physicians look at sore throats every day; taking a few extra minutes to do a thorough oral examination could benefit the patient. If primary care physicians joined in routinely screening for oral cancer, long-term survival rates would undoubtedly have a potential room to improve as one reviewer concluded.

Methods of screening

Abundant reports were documented regarding miscellaneous methods of oral cancer detection and screening in the following paragraph.[14,18-22] Physical examination includes a self-examination and clinical examination. Clinicians have a responsibility to perform a thorough head and neck examination as part of the physical assessment of their patients. It takes less than 2 minutes to perform. The goal of examination is to detect any nodules, swellings, mucosa alterations (ulcerations, textural or color changes) and unexplained lymph adenopathy. While many routines exist for an oral examination, each clinician must develop his or her own method, uses it in all patients, and carefully documents positive findings. Toluidin blue staining is an easy simple method with the dye having affinity to cancer cells. Commercial kit with protocol is available for a large scale screening of high-risk population or in clinical patients by topical application or mouth rinsing. Yet for candidates having oral field cancerization, rinsing or gargling is recommended. However, a significant percentage of false negative and false positive still exist. Meanwhile, a biopsy is still needed before a diagnosis can be confirmed. An excisional biopsy is definitely sufficient for pathological analysis of a small 0.5 to 1 cm lesion. However, multiple incisional biopsy is more appropriate in a large lesion, which may also be stained with TB to define highly suspected locations with priority of biopsy. It is quite often that the cases encountered had no definite locations of lesion but presented with a picture of

panoral premalignant cancerization in high-risk patients with a history of BQ use and smoking for 20 to 30 years.[11,14] It can be difficult to perform an incisional biopsy at precisely suspected locations in such conditions. Therefore, some researchers or clinicians claimed at using an alternative method of sceening by exfoliative cytology collected by tissue scraping. However, exfoliative cytology in the screening for oral cancer has never achieved the same success as it has for diagnosing cancer of the uterine cervix. Oral exfoliative cytology enjoyed much attention in the 1960s, eventually falling from favor, due largely to the subjective nature of its interpretation. Yet the recent application of quantitative and immumocytochemical techniques has, to some extent, refined its potential role. However, the absence of a marker, present in all malignant lesions but never seen in benign lesions, limits its clinical utility.[14,20] The other reason of drawbacks of exfoliative cytology for screening oral cancer was that the lesion still had to be identified or anatomically located for biopsy confirmation before a surgery can be initiated. Technical problems may also easily be encountered in cases with field cancerization in the BQ chewer.[11,12,23] Pure salivae being secreted from the major or minor salivary glands without cellular content hasn't been proved to have any contribution for cancer detection. However, salivae containing the exfoliated cells from scraping or natural exfoliation combining with cytospin may provide another way of approaching. Utilizing cytospin preparation from the saliva may potentially increase the collected cellular contents for analysis. Some oral cancer cytokeratin markers have been detected occasionally at a higher level within serum in few oral cancer patients. However, unlike AFP for hepatoma or some important markers for prostate or other cancers, there is no one specific marker can be universally accepted or used for detection of oral cancer. Lacking of profound hepatic sinusoid circulation, the superficially located oral cancer or precancer lesions did not give a promising result so far.[12,14,18] The future role for oral exfoliative cytology—bleak or bright? It may well be accepted that a more scientific and efficient way of oral exfoliative cytology might enjoy a greater success based on the understanding of the molecular mechanisms and characteristics of cancer development.

Mechanisms of oral cancer formation

Similar to a well-established colorectal carcinoma model, oral cancer is also considered to be a multi-hit process involving a number of aberrant genetic events culminating in malignant transformation at the molecular and biological levels. It is well known that following the action of various carcinogens (chemical, physical, biological) on normal cells, a long period (latency) of several months to years (10 months-30 years) in humans occurs between development of precancer cells and their transformation into cancer cells. However, the molecular and biological events that take place within the precancer cells during this quiescent stage are not yet fully understood. Recent studies revealed that preneoplastic development and transforma-

tion into cancer cells is determined initially by genetic (oncogenes, anti-oncogenes) changes, with sequential multiple somatic mutations, and later by epigenetic or environmental cell factors such as hormones, growth factors (GFs), cytokines, vitamins, and prostaglandins (PGs). These factors can markedly change the evolution of preneoplastic cells by enhancing, retarding, or inhibiting their transformation into cancer cells, or even reversing them to a normal phenotype [1,2,15,23]. These effects act on DNA, RNA, and protein synthesis, as well as on cell replication, cell cycles, cell surfaces, and intercellular communications. Therefore, these abnormal DNA, oncogenes or tumor suppressor genes, and ultrastructural intracellular or cell surface antigenic determinants as potential biomarkers are essential for early detection of preneoplastic cells and cancer cells. A significant advancement recently is the gradual understanding of the molecular mechanism of cancer formation. Although, a universal tumor marker is still lacking, a combination of several markers may be useful and more accurate than ever. In particular, the last 10 years has seen a shift in diagnostic methods from the histopathological to the molecular level.[24-29] It is accepted that oral exfoliative cytology can not only assume a greater role by providing samples of DNA for genetic analysis but also can provide an useful tool for screening. The pendulum swings from the morphological picture towards the molecular level, we may yet see a new role for exfoliative cytology. Greater understanding of genetic aberrations may predict not only the biological behavior of the tumor but its likely response to both traditional and novel forms of therapy. It remains to be seen if exfoliative cytology can take further step from research tool to that of routine clinical practice.[22]

New markers and tools for oral cancers detection

With advancement in modern molecular biology technique, a lot more new markers in oral cancer were studied and found. Significant momentum has been devoted to the exploration in ras oncogenes, P53, P16 tumor suppressor genes, and the abnormality of other genes such as cyclin-D1, retinoids or retinoic acid nuclear receptors, telomerase, and so on in many cancer research groups. For example, using in-situ hybridization and TRAP assay, a gradual increase of telomerase activity in the malignant transformation process was confirmed in oral cancer and precancer.[29] Loss RAR-β expression in the malignant transformation of oral cancer has been reported by analyzing the expression of RAR-β using *In situ* hybridization (ISH) with RAR-β antisense riboprobe in oral cancer and adjacent non-cancerous matched tissues (NCMT) to correlate with their clinico-pathological features.[27,28] With the great advancement in disclosing the pieces of puzzle of cancer development, next generations of cancer screening methods will favor a more efficient and reliable tool based on previous contribution of scientists. The newly developed microarray/gene chip technology with more reliable/predictable tumor markers will encourage us to seek for a new approach for cancer screening.[30]

However, the program of detection and screening of cancers seeming like a war, should be based on full government support, cooperation of school education, news media, medical services, and the general awareness from the whole population. Care should especially be taken in the policy or strategy planning and performing the cancer detection/screening programs. As a dentist as well as health care worker, we need to know the important roles of our profession in the screening and detection of oral cancer.

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口腔癌及癌前期病變之偵測與篩檢

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摘 要

口腔癌是一種具致命性的疾病，其好發率約佔台灣男性惡性腫瘤的第五位，全人口惡性腫瘤的第七位。在台灣地區有兩百五十萬抽煙及嚼食檳榔的高危險群是口腔癌高度盛行的主因。遺憾的是，越來越多在醫學中心診斷出的新病例皆是屬於口腔癌分期的第三期及第四期。這些現象讓我們體會到，針對高危險群作早期預防、正確篩檢與及時治療是一樣重要的。在這篇文獻回顧中，我們概括地描述口腔癌的病程且探討對於這個疾病篩檢的重要性，並著重介紹一些傳統以及最新的口腔癌篩檢方法。

關鍵詞：口腔癌，篩檢，預防，腫瘤標記，細胞學，檳榔。

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