Expert Consensus on the Detection and Screening of Oral Cancer and Precancer

Shou Yen KAO[1], Li MAO[2], Xin Chun JIAN[3], Gunaseelan RAJAN[4], Guang Yan YU[5]

Oral cancer is an aggressive disease with a high incidence in both males and females in Asia and ranks as the first of all malignancies in India. The relatively high prevalence rate of oral cancer in Asia is mainly due to the fact that a high percentage of the population are smokers or chew betel nut. They comprised the so called 'high risk population' of oral cancer. Meanwhile, epidemiological surveys showed a much lower 5-year survival rate in patients with advanced TNM stage III and IV oral cancer than those in the earlier stage I and II disease after treatment. Therefore, it is important to identify and treat precancerous lesions and oral cancer at early stages. In this article, we describe the expert consensus contributed by outstanding clinicians and scientists at the 11th Asian Congress of Oral & Maxillofacial Surgery (ACOMS) and we highlight the importance of oral cancer screening by various conventional and novel methods based on scientific research.

Key words: *Asia, betel nut, oral cancer, screening, smoking*

Oral cancer is the fifth most common cancer in the world, accounting for 412,000 new cases and 262,000 deaths annually since 1985, four-fifths of what occurred in the developing regions. In South Asia, oral cancer ranks as the first amongst all types of cancers in males and the third in females[1,2]. Oral cancer is associated with chronic irritating factors such as tobacco, smoking, alcohol and betel quid (BQ) use. While cigarette smoking and alcohol drinking are major risk factors in Western countries, betel quid use and smoking are major aetiologic factors of oral cancer in South Asia, Southeast Asia and Taiwan[1-3]. Unfortunately, a higher rate of incidence of oral cancer and a higher mortality rate have been shown to correlate with the increasing prevalence rate of betel chewing in this area. For hundreds of years, betel chewing in Asia has been generally accepted as a social custom or behaviour. Previous epidemiological studies reported that the incidence of oral squamous cell carcinoma (OSCC) in BQ users and smokers was more than 100 times higher than the general population[3,4]. There is abundant literature clarifying the roles of ingredients of BQ-related carcinogenesis. It is generally agreed that BQ can potentially damage the oral mucosa to induce genotoxic or non-genotoxic effects, which may further contribute to initiation, promotion and progression of oral cancer. Various ingredients in BQ, including areca nuts, nitroso-derivatives, arecoline, safrole, lime and so on, have been extensively studied and linked to carcinogenic effects, co-carcinogenic effects and tumour promotion[3,5-10].

In addition to oral cancer, other betel quid-associated diseases in the oral cavity such as mucositis, submucous fibrosis, severe tooth attrition and periodontitis have been difficult to manage, which has presented a great challenge for the general healthcare system. Currently,

1 Professor and Chair, Department of Stomatology, Taipei-Veterans General Hospital, School of Dentistry, Yang-Ming University, Taipei.
2 Professor and Chair, Department of Oncology and Diagnostic Science, School of Dentistry, University of Maryland, Maryland, USA.
3 Professor, Department of Oral and Maxillofacial Surgery, Xiangya Hospital, Central South University, Changsha, Hunan Province, P.R. China.
4 Clinical Professor, Rajan Dental Hospital, Adjunct professor, Tamil Nadu Dr. MGR Medical University, Chennai, India.
5 Professor, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, P.R. China.

Corresponding author: Dr Shou Yen KAO, Professor and Chair, Department of Stomatology, Taipei-Veterans General Hospital, Shih-Pai Road, Sec-2, No 201, Taipei, Taiwan. Tel: 886-2-28757013; Fax: 886-2-28742375; Email: sykao@vghtpe.gov.tw
Co-corresponding author: Dr Li MAO, Professor and Chair, Department of Oncology and Diagnostic Science, School of Dentistry, University of Maryland, 650 West Baltimore Street, Baltimore, Maryland 21201, USA. Email: lmao@umaryland.edu

in developing countries, more than 50% of oral cancer patients are diagnosed as stage III or IV during their first visit to a healthcare facility. Unfortunately, the overall 5-year survival rate of these patients will be poor despite recent advances in surgery, radiotherapy and chemotherapy[4]. Furthermore, the cost of treatment in stage III or IV cases is far more than the cost of treatment in stage I or II cases. In the 11th Asian Congress of Oral & Maxillofacial Surgery (ACOMS) in Xi'an, China (Aug 22 to 25, 2014), an expert consensus on the detection and screening of oral cancer and precancer was conducted by outstanding clinicians and scientists from Asia and the United States. It was unanimously agreed that an efficient detection and screening programme allows the correct diagnosis of lesions at the pre-cancer stage or in early stages of oral cancer. Proper treatment can then be given to these patients to increase their survival. The Xi'an consensus highlights the importance of oral cancer and pre-cancer screening by various conventional and novel methods based on scientific research. This article reviews the related literature and discussions, which were addressed at the consensus meeting.

Screening the high risk population

Oral cancer is curable if it can be diagnosed and treated early enough. Amongst human cancers, oral cancer is one of few with a vast potential for early detection. Given the lack of successful strategies for oral cancer prevention so far, the priority should be focused on screening. The feasibility of oral cancer screening is largely based on the fact that the oral cavity can be easily accessed visually. Various programmes or policies have been supported by a number of governmental agencies worldwide for detecting oral cancer in the past decade. To cope with this, funding from these governmental agencies have been distributed to various organisations and healthcare professionals such as general health auxiliaries in the public first-line health care institute, dentists and ENT (Ear, Nose, and Throat) doctors in medical centers[3,4]. However, the long-term effects of these efforts remains to be seen. Previous reports revealed that 90% of male oral cancer patients were betel quid chewers and smokers in South and Southeast Asia. Undoubtedly this high-risk group of betel chewers and smokers, accounting for the main prevalence of oral cancer should be screened with priority. Meanwhile, a follow-up system should be established to recall and monitor the patients with oral cancer or with precancer lesions after diagnosis and treatment because of the high incidence of second primary tumours in oral cancer patients and high malignant transformation rate of patients with precancerous lesions[11-14].

Malignant transformation of precancerous lesions

Attention should specifically be focused on patients with precancerous lesions[11-14]. Although the potential of malignant transformation for patients with erythroplakia is higher than patients with leukoplakia, oral leukoplakia is far more common. Some of the patients are idiopathic while the others exhibited habits such as smoking tobacco, drinking alcohol or using BQ. About 80% of patients with leukoplakias are in fact at low risk of developing OSCC with no evidence of dysplasia in the lesions, whereas others may eventually transform into OSCC[12]. Unfortunately, there is currently no histological or alternative means which can reliably predict which leukoplakia is indeed premalignant. Overall the rate of malignant transformation of oral leukoplakia is about 3% to 6% over 10 years, although much higher rates have been reported, which is largely dependent on the populations surveyed and the rigour of follow-up care performed. Medical management of leukoplakia includes reducing or quitting habits related to risk factors, increasing the intake of fruit and vegetables in the diet, lesion removal and possibly the use of active agents[13]. Retinoids, carotenoids and topical cytotoxic agents have been tried to treat oral leukoplakia and to prevent OSCC development with limited success. Newer therapies developed from frontier and novel research are still on the horizon[13,15-17].

Roles of healthcare workers

Healthcare workers or auxiliaries need to clearly understand their roles in cancer screening. One may argue that oral cancer screening is not necessary because routine dental examinations already include a full oral mucosa examination. However, apart from the fact that more than 50% of the adult population do not visit a dentist annually in many developing countries, there is evidence which suggests that many oral cancer cases are missed by healthcare professionals including dental practitioners[14,18]. Many reasons may contribute to this outcome including the inability to recognise early lesions, the innocuous appearance of the lesions or lesions without morphological changes before the development of invasive cancers, plus a lack of experience from clinicians. Therefore, other professions or specialties should also be included in the screening programme. Nevertheless, screening for oral cancer can be a simple and non-invasive procedure, which can be integrated into

the comprehensive assessment of older patients or high-risk populations who account for the major part of the oral cancer patients. Furthermore, other medical specialties might feel comfortable performing an oral cancer screening examination[13,14,18-20]. Since 5-year survival rates are far greater in individuals with localised OSCC than in those with metastatic diseases, the detection of early oral cancer can make a significant difference for patients' outcomes[21]. The elderly, who are at risk of oral cancer might visit their dentists far less frequently than they visit their physicians[20]. The primary physicians examine sore throats routinely. Therefore, taking a few extra minutes to do a thorough oral examination may help improve early detection of oral cancer. If primary care physicians can join in the routine screening of oral cancer, long-term survival rates of oral cancer patients may improve as more early oral cancers can be detected.

Methods of screening

Numerous reports have documented methods of oral cancer detection and screening[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 min to perform. The goal of the examination is to detect any nodules, swellings, mucosa alterations (ulcerations, textural or colour changes) and unexplained lymph adenopathy. While many routines exist for an oral examination, each clinician must develop his or her own method, use it in all patients, and carefully document positive findings. Toluidine blue staining is an easy simple method with the dye showing affinity to cancerous mucosa or lesions with dysplastic changes. A commercial kit with a protocol is available for large-scale screening of high risk populations or in clinical patients by topical application or mouth rinsing. Yet for candidates who have field cancerisation in the oral cavity, rinsing or gargling is recommended. However, there is a significant percentage of false negative and false positive results that exist[23]. Meanwhile, a biopsy is still needed before a diagnosis can be confirmed. An excision biopsy is typically sufficient for pathological analysis of small 0.5 to 1.0 cm lesions. However, incision biopsy at multiple locations may be necessary for large lesions. For most cases encountered, there was no definite location of lesion but there was panoral premalignant cancerisation in high-risk patients with a history of BQ use and who had smoked over a 20 to 30 year period[11,14]. It can be difficult to perform an incision biopsy at precisely suspected locations in such conditions. Therefore, some researchers or clinicians advocate the use of an alternative method for screening, by collecting exfoliated cells through tissue scraping. However, exfoliated cell cytology in the screening for oral cancer has never achieved the same success as it has for diagnosing cancer of the uterine cervix. Oral exfoliated cell cytology enjoyed much attention in the 1960s, eventually falling out of favour, due largely to the subjective nature of its interpretation. Yet the application of quantitative and immunocytochemical techniques has, to some extent, refined its potential role. However, the absence of a validated marker, present in all malignant lesions but never seen in benign lesions, limits its clinical utility[14,20]. The other drawback of exfoliated cell cytology for screening oral cancer is that the location of cancerous lesions may be difficult to identify, and to allow biopsy and pathological confirmation. Technical problems may also be easily encountered in cases with field cancerisation in the BQ chewers[11,12,23]. Saliva being secreted from the major or minor salivary glands without cellular content was considered to have no value for cancer detection. However, saliva containing the exfoliated cells from scraping or natural exfoliation combined with cytospin may improve its value in oral cancer detection. Utilising cytospin preparation from the saliva may potentially increase the collected cellular content for analysis. However, unlike alpha-fetoprotein (AFP) for hepatoma, protein specific antigen (PSA) for the prostate or specific biomarkers for other cancers, no specific marker, which has received universal acceptance from the scientific community, are available for the detection of oral cancer. It may well be accepted that a more scientific and efficient way of oral exfoliated cell cytology might offer greater success, based on the understanding of the molecular mechanism and characteristics of cancer development. The future role for oral exfoliated cell cytology – bleak or bright – remains to be determined.

Mechanisms of oral cancer formation

Analogous to a well-established colorectal carcinoma model, oral cancer is also considered to be a multi-hit process involving a number of aberrant genetic and epigenetic events culminating during the tumorigenic process. 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 to 30 years) in humans occur between the development of precancerous cells and their transformation into cancer cells. However, the molecular and biological events that take place within the precancerous cells during this quiescent stage are not yet fully under-

stood. Many studies revealed that development of precancerous cells and their transformation into cancer cells are determined initially by genetic (oncogenes and antioncogenes) changes including multiple somatic mutations as well as epigenetic alterations, in order to impact cellular 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 into a normal phenotype[1,2,15]. 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 tumour suppressor genes, and ultrastructural intracellular or cell surface antigenic determinants as potential biomarkers are essential for the early detection of preneoplastic cells and cancer cells. Although, a universal tumour marker might still be lacking, a combination of several markers may be useful and more accurate than ever. In particular, the last 20 years has seen a shift in diagnostic methods from the histopathological to the molecular level[24-37]. It is expected that oral exfoliated cell cytology may not only assume a greater role by providing samples of DNA for genetic analysis but also can provide a useful tool for screening.

New markers and tools for oral cancer detection

Over the past four decades, given that the 5-year survival rate has not improved for oral cancer patients, we believe the research priorities should explore the mechanism to find out new approaches for early diagnosis and novel therapy[27]. With improved understanding of the underlying molecular features and biology in oral tumorigenesis, new biomarkers and molecular targets for oral cancer have been identified in the last decade. Significant momentum has been devoted to the exploration in Ras oncogenes, p53, p16 tumour suppressor genes, abnormal expression of other genes such as cyclin-D1, retinoids or retinoic acid nuclear receptors, telomerase, and more recently the identification of common genetic alterations of PI3K and Notch1 genes[28-33,38,39].

The follow-up of treated oral cancer cases is equally important to the screening of fresh cancer cases. Different from laryngeal or hypopharyngeal cancers, the predisposed relapse or recurrence of oral cancers tends to occur in the oral cavity. Beyond conventional staining dye by direct visual detection[23], the use of narrow band imaging (NBI) was recently proposed as a useful method for early detection of precancer and recurrent or second primary lesions in treated cancer cases[34]. With the great advancement in understanding cancer development, subsequent generations of cancer screening methods will favour a more efficient and reliable tool based on previous contributions of scientists. The newly developed microarray/gene chip technology with more reliable/predictable tumour markers will encourage us to seek new approaches for cancer screening[35-37]. Recent novel research reports suggest the potential importance of new biomarkers of microRNAs in the cancer progression. Two important new biomarkers miRNA-21 and miRNA-31 have recently been found to increase in the plasma and saliva of oral cancer patients. The levels of miRNA-31 in the plasma and saliva, especially, correlate well with a tumour burden. In other words, the biomarker miRNA-31 in plasma and saliva significantly decreases after tumour ablation surgery. The levels of miRNA-21 and miRNA-31 not only increase in invasive oral cancer, but also in oral precancer lesions[40-42]. This highlights a breakthrough in the early detection of oral precancer/cancer from saliva/plasma.

We propose that the early detection and screening of cancer is an ongoing battle which should be fought on all fronts with the full support and cooperation of governmental agencies, school educators, the mass media, medical professionals and the general public.

References

1. Boyle P, Macfarlane GJ, Maisonneuve P, Zheng T, Scully C, Tedesco B. Epidemiology of mouth cancer in 1989: a review. J R Soc Med 1990;83:724–730.
2. Johnson NW. Orofacial neoplasms: global epidemiology, risk factors and recommendations for research. Int Dent J 1991;41:365–375.
3. Ko YC, Huang YL, Lee CH, Chen MJ, Lin Lm, Tsai CC. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. J Oral Pathol Med 1995;24:450–453.
4. Chen YK, Huang HC, Lin LM, Lin CC. Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan. Oral Oncol 1999;35:173–179.
5. Liu TY, Chen CL, Chi CW. Oxidative damage to DNA induced by areca nut extract. Mutat Res 1996;367:25–31.
6. Kuo MY, Jeng JH, Chiang CP, Hahn LJ. Mutations of Ki-ras oncogene codon 12 in betel quid chewing-related human oral squamous cell carcinoma in Taiwan. J Oral Pathol Med 1994;23:70–74.
7. Jin YT, Tsai ST, Wong TY, Chen FF, Chen RM. Studies on promoting activity of Taiwan betel quid ingredients in hamster buccal pouch carcinogenesis. Eur J Cancer B Oral Oncol 1996;32B:343–346.
8. Wang CK, Peng CH. The mutagenicities of alkaloids and N-nitrosoguvacoline from betel quid. Mutat Res 1996;360:165–171.
9. Wang CK, Wu MJ. The separation of phenolics from piper betel leaf and the effect on the mutagenicity of arecoline [In Chinese]. J Chin Agric Chem Soc 1993;34:638–647.
10. Lee-Chen SF, Chen CL, Ho LY, et al. Role of oxidative DNA damage in hydroxychavicol-induced genotoxicity. Mutagenesis 1966;11:519–523.
11. Shiau YY, Kwan HW. Submucous fibrosis in Taiwan. Oral Surg Oral Med Oral Pathol 1979;47:453–457.

12. van der Waal I, Schepman KP, van der Meij EH, Smeele LE. Oral leukoplakia: a clinicopathological review. Oral Oncol 1997;33:291–301.
13. Scully C. Oral precancer: preventive and medical approaches to management. Eur J Cancer B Oral Oncol 1995;31B:16–26.
14. Speight PM, Zakrzewska J, Downer MC. Screening for oral cancer and precancer. Eur J Cancer B Oral Oncol 1992;28B:45–48.
15. Lupulescu AP. Control of precancer cell transformation into cancer cells: its relevance to cancer prevention. Cancer Detect Prev 1996;20:634–637.
16. Breitman TR, Selonick SE, Collins SJ. Induction of differentiation of the human promyelocytic leukemia cell line (HL-60) by retinoic acid. Proc Natl Acad Sci U S A 1980;77:2936–2940.
17. Hong WK, Lippman SM, Itri LM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990;323:795–801.
18. Franceschi S, Barzan L, Talamini R. Screening for cancer of the head and neck: if not now, when? Oral Oncol 1997;33:313–316.
19. Sankaranarayanan R. Health care auxiliaries in the detection and prevention of oral cancer. Oral Oncol 1997;33:149–154.
20. Fedele DJ, Jones JA, Niessen LC. Oral cancer screening in the elderly. J Am Geriatr Soc 1991;39:920–925.
21. Chiodo GT, Eigner T, Rosenstein DI. Oral cancer detection: The importance of routine screening for prolongation of survival. Postgrad Med 1986;80:231–236.
22. Ogden GR. The future role for oral exfoliative cytology-bleak or bright? Oral Oncol 1997;33:2–4.
23. Chen YW, Lin JS, Fong JH, et al. Use of methylene blue as a diagnostic aid in early detection of oral cancer and precancerous lesions. Br J Oral Maxillofac Surg 2007;45:590–591.
24. Latif F, Fivash M, Glenn G, et al. Chromosome 3p deletions in head and neck carcinomas: statistical ascertainment of allelic loss. Cancer Res 1992;52:1451–1456.
25. Shao ZM, Dawson MI, Li XS, et al. p53 independent G0/G1 arrest and apoptosis induced by a novel retinoid in human breast cancer cells. Oncogene 1995;11:493–504.
26. Bollag W, Peck R, Frey JR. Inhibition of proliferation by retinoids, cytokines and their combination in four human transformed epithelial cell lines. Cancer Lett 1992;62:167–172.
27. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
28. Hu L, Crowe DL, Rheinwald JG, Chambon P, Gudas LJ. Abnormal expression of retinoic acid receptors and keratin 19 by human oral and epidermal squamous cell carcinoma cell lines. Cancer Res 1991;51:3972–3981.
29. Mao L, Lee JS, Fan YH, et al. Frequent microsatellite alterations at chromosomes 9p21 and 3p14 in oral premalignant lesions and their value in cancer risk assessment. Nat Med 1996;2:682–685.
30. Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. Science 2011;333:1157–1160.
31. Agrawal N, Frederick MJ, Pickering CR, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 2011;333:1154–1157.
32. Song X, Xia R, Li J, et al. Common and complex Notch1 mutations in Chinese oral squamous cell carcinoma. Clin Cancer Res 2014;20:701–710.
33. Izumchenko E, Sun K, Jones S, et al. Notch1 mutations are drivers of oral tumorigenesis. Cancer Prev Res (Phila) 2015;8:277–286.
34. Chu PY, Tsai TL, Tai SK, Chang SY. Effectiveness of narrow band imaging in patients with oral squamous cell carcinoma after treatment. Head Neck 2012;34:155–161.
35. Saintigny P, Zhang L, Fan YH, et al. Gene expression profiling predicts the development of oral cancer. Cancer Prev Res (Phila) 2011;4:218–229.
36. Kawaguchi H, El-Naggar AK, Papadimitrakopoulou V, et al. Podoplanin: a novel marker for oral cancer risk in patients with oral premalignancy. J Clin Oncol 2008;26:354–360.
37. Hu S, Arellano M, Boontheung P, et al. Salivary proteomics for oral cancer biomarker discovery. Clin Cancer Res 2008;14: 6246–6252.
38. Chang LY, Lin SC, Chang CS, et al. Telomerase activity and in situ telomerase RNA expression in oral carcinogenesis. J Oral Pathol Med 1999;28:389–396.
39. Toulouse A, Loubeau M, Morin J, et al. RARbeta involvement in enhancement of lung tumor cell immunogenicity revealed by array analysis. FASEB J 2000;14:1224–1232.
40. Liu CJ, Kao SY, Tu HF, Tsai MM, Chang KW, Lin SC. Increase of microRNA miR-31 level in plasma could be a potential marker of oral cancer. Oral Dis 2010;16:360–364.
41. Liu CJ, Lin SC, Yang CC, Cheng HW, Chang KW. Exploiting salivary miR-31 as a clinical biomarker of oral squamous cell carcinoma. Head Neck 2012;34:219–224.
42. Liu CJ, Tsai MM, Hung PS, et al. miR-31 ablates expression of the HIF regulatory factor FIH to activate the HIF pathway in head and neck carcinoma. Cancer Res 2010;70:1635–1644.