New Hope for an Oral Cancer Solution: Together We Can Make a Difference

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SOMMAIRE

On attribue au cancer de la bouche des taux de mortalité et de morbidité élevés, principalement à cause du retard du diagnostic. Bien que les dentistes soient formés à identifier les lésions malignes et prémalignes, on a besoin d'un système organisé pour orienter les patients et améliorer l'accès aux spécialistes dans les domaines du diagnostic et de la prise en charge de ces lésions. Dans le présent article, nous décrivons comment le Programme de prévention du cancer de la bouche de la Colombie-Britannique (BC OCPP) relève ce défi en établissant des liens entre les cabinets dentaires et les centres d'aiguillage de la collectivité. Ces liens créent des partenariats entre les scientifiques et les cliniciens, et de nouvelles technologies ont vu le jour pour améliorer le diagnostic précoce. Un large spectre d'intervenants a été engagé pour assurer un dépistage communautaire, et des initiatives d'approche provinciales, nationales et internationales ont été lancées.

Pour les citations, la version définitive de cet article est la version électronique : www.cda-adc.ca/jcda/vol-74/issue3/261.html

> *Screening is more than an exam: it is a process. Clinically it involves patient communication, diagnostic work-up and management and quality control. It also involves development of creative strategies for removing barriers... technology development can drive such activity. Teamwork is critical in making this happen.*
>
> — The BC OCPP

Oral cancer represents a significant challenge worldwide, with close to 300,000 cases identified each year.[1] Mortality and morbidity rates associated with oral cancer are high, largely as a result of late diagnosis, and only small improvements in outcome have been achieved over recent decades. Dentists need to play a role in establishing a new paradigm for oral cancer control.

Dental practitioners are trained to diagnose premalignant and malignant lesions, and individual dentists have been making these diagnoses for years. However, there has been no agreement on who and how to screen for oral cancer or on when and where to refer patients for management. As a result, the problem of late diagnosis has not been addressed. We need an organized system to offer guidance and to improve access

to experts in diagnosis and management of these lesions.

The British Columbia Oral Cancer Prevention Program (BC OCPP) is addressing this challenge through a multifaceted program. The program is anchored by a clinical infrastructure that links community dental practices and referral centres to improve detection, risk assessment and management of oral cancers and premalignant lesions.[2] Partnerships between scientists and clinicians have produced new technologies aimed at removing barriers to early diagnosis. In this article, we describe these initiatives and the future plans of the BC OCPP for provincial, national and international outreach.

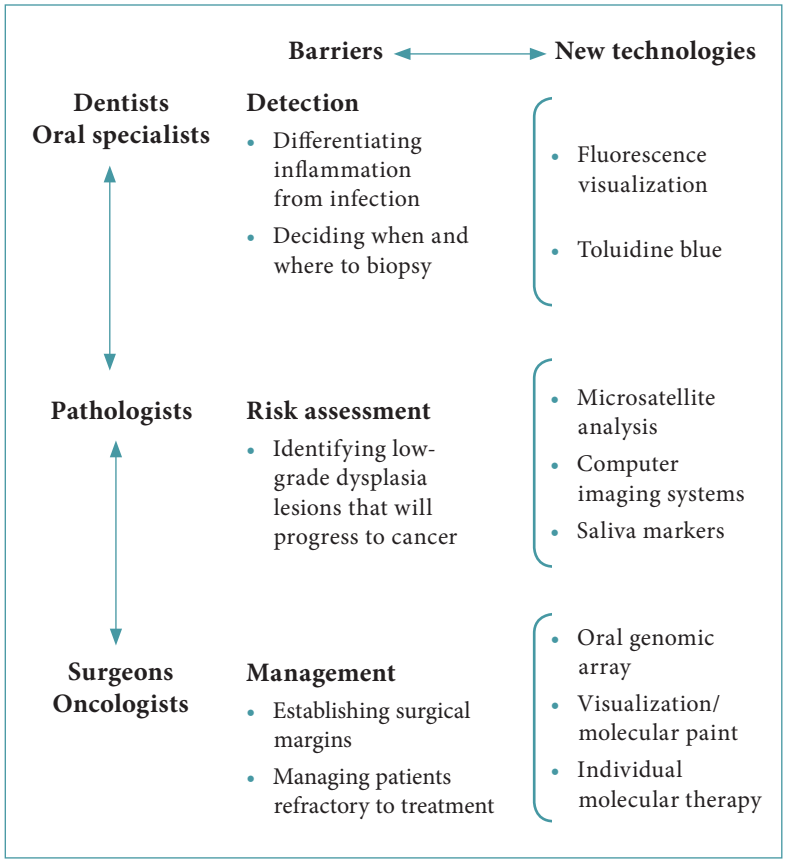

Figure 1: Tools to overcome barriers to screening for oral disease at detection, risk assessment, and management and referral levels.

Our History: The Evolution of the BC OCPP

The BC OCPP has evolved through the stepwise addition of a number of critical components leading to a formal program in 1999. The process began in 1992 with a partnership between the BC Oral Biopsy Service (OBS) and scientists at the BC Cancer Agency to identify molecular predictors of cancer risk in patients referred to the OBS by community dentists. The OBS has a long history (since 1980) of providing centralized oral pathology review for community dentists. In 1999, on the basis of these early studies, funding was obtained from the National Institute of Dental and Craniofacial Research, within the National Institutes of Health in the United States, to launch a longitudinal study aimed at developing biomarkers and improving our ability to assess and manage patients. That year, the first dysplasia clinic was established to coordinate this activity. Now, there are 5 clinics and plans for continued expansion across the province.

New Screening Technologies: A Driving Force for Change

Early in the development of the BC OCPP, several major barriers to the *detection*, *risk assessment* and *management* of early disease were identified (**Fig. 1**). Oral premalignant lesions and early cancer vary considerably in clinical appearance and often resemble benign conditions, making clinical *detection* difficult. Currently, the risk of premalignant lesions progressing to cancer is assessed histologically. A high-grade lesion (severe dysplasia and carcinoma in situ) indicates a high risk of cancer development. Our longitudinal study has shown that most of these lesions progress to invasive cancers; hence, we recommend treatment. Most low-grade lesions (mild and moderate dysplasia) do not progress to cancer. A major barrier in *risk assessment* is to identify the small proportion of these low-grade lesions that will progress into cancer. Finally, oral premalignant lesions and cancer frequently extend beyond the boundary of the clinically visible lesion. A major barrier in their *management* is to identify the extent of the lesions to facilitate complete removal.

These barriers have stimulated the development and validation of new technologies, some of which are shown in **Fig. 1** and described briefly here.

Fluorescence Visualization

This approach uses a hand-held device to directly detect alterations in normal autofluorescence that are associated with morphologic and biochemical changes to tissue during cancer development. In dysplasia clinics, fluorescence visualization has proved valuable in the detection of high-risk lesions, in the delineation of surgical margins and in follow-up after treatment.[3,4] The approach is only now being evaluated for detection in community settings.

Toluidine Blue

Toluidine blue has a long history and established validity in the detection of oral cancers but its value in identifying oral premalignant lesions has been contentious, as not all such lesions stain with the dye. We have shown that tolui-

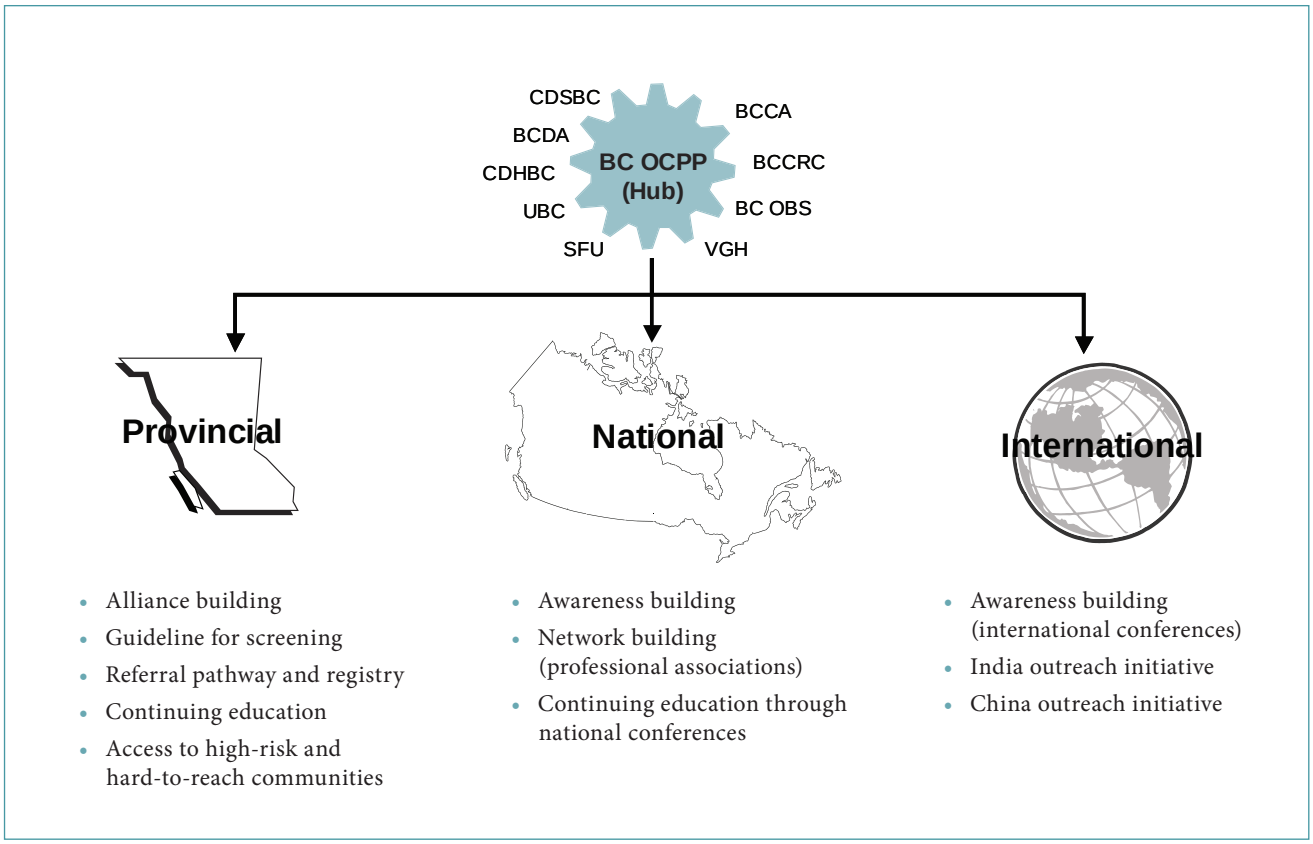

Figure 2: Creating a network to achieve population-based oral cancer screening. The BC OCPP's organizational hub is linked with a broad range of stakeholders.

Note: BCCA = BC Cancer Agency, BCCRC = BC Cancer Research Centre, BC OBS = BC Oral Biopsy Service, VGH = Vancouver General Hospital, SFU = Simon Fraser University, UBC = University of British Columbia, CDHBC = College of Dental Hygienists of British Columbia, BCDA = British Columbia Dental Association, CDSBC = College of Dental Surgeons of British Columbia.

dine blue staining of oral premalignant lesions correlates with the presence of high-risk molecular patterns and with progression to cancer, and that this relationship holds true for both low- and high-grade dysplasia.[5] This approach is used routinely in our dysplasia clinics for detection and risk assessment.

Microsatellite Analysis

The development of oral cancer requires the accumulation of multiple genetic alterations. Detection of these alterations can be a powerful predictor of risk of premalignant lesions progressing to cancer. One of the more promising approaches is assessment of tissue for loss of heterozygosity. We have found 3 loss of heterozygosity patterns that separate low-grade lesions into different levels of risk of progression to cancer[6–9] and cancer recurrence after treatment.[10] These patterns are being validated in the ongoing longitudinal study that is being conducted at the dysplasia clinics.

High-Resolution Computer Imaging Systems

Conventional histologic assessment of a biopsy sample relies on detecting specific visible features (such as dysplasia) and the degree of epithelial involvement.[11] High-resolution computer imaging systems reveal these features in greater detail, as well as the frequency and distribution of such changes in cells. These systems are being applied to assess both tissue samples and exfoliated cells. Preliminary studies have shown that such imaging can identify nuclear changes in low-grade dysplasia that are associated with the presence of high-risk molecular clones and with risk of cancer formation.[12]

Saliva Markers

Currently, a large amount of research is focused on the identification of genetic changes in saliva samples to determine whether they can be used to detect cancer and premalignant disease.[13,14] This is a promising noninvasive approach, which is still in an early stage of development. We plan to validate these markers in patients seen at the dysplasia clinics.

Genomic Profiling for Patient Management

We are developing a miniaturized gene chip called the OPL (oral premalignant lesion) Risk Prediction chip to analyze very small biological samples, such as those collected from patients during longitudinal monitoring. The

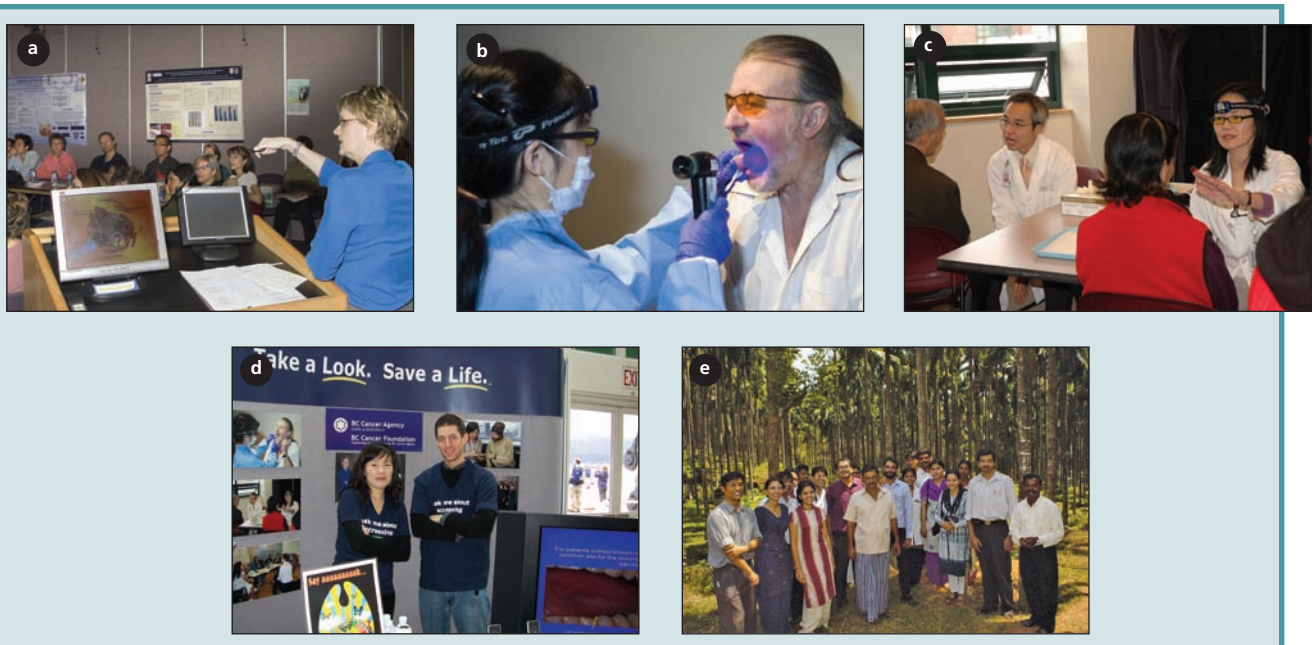

Figure 3: The outreach activities of the BC OCPP, which extend to the provincial, national and international levels, include: **(a)** Partnership with community dentists — continuing education for knowledge transfer and network building. **(b)** Outreach through community screening in a high-risk, medically underserved area in Vancouver's Downtown Eastside. **(c)** Partnership with community representatives to provide oral cancer screening in local health fairs for the elderly Chinese in Chinatown, Vancouver. **(d)** Awareness building and continuing education at the Pacific Dental Conference, one of the largest dental conferences in North America. **(e)** Oral cancer screening camps conducted by the Manipal College of Dental Sciences, Mangalore, in rural villages of India. Source: BC OCPP (www.orcanet.ca).

information will improve the prediction of risk of progression.[15] It will also be used in patient management to design molecular probes that can be painted in the patient's mouth to track the spread of genetically altered cells and to guide the selection of individualized drug interventions specific to molecular alterations within the tumour.

Our Future: Movement to a Province-Wide Screening Program

To have an impact on the incidence of oral cancer, a broad range of stakeholders must be involved, including (but not limited to) professional societies, educational institutions, health care facilities, government and the public. A combined effort will guide the evolution of oral cancer screening toward population-based coverage. Creating such a network is becoming a key function of the BC OCPP (**Fig. 2**). Activities that require these alliances include the standardization of screening activities in the dental community and their integration into day-to-day practice, the further evolution of referral and management infrastructures and the development of strategies for population-based screening (**Fig. 3**).

Central to the standardization of screening activity is the provision of guidelines for the early detection of oral cancer with step-by-step procedures for the assessment of clinical lesions, for obtaining oral mucosal tissue samples and interpreting biopsy results. Such guidelines are included in this issue of the *JCDA*.[11,16] Also included is information on strategies for communicating better with the patient about screening[17] and on follow-up of abnormalities,[11] often requested by dentists. This issue also includes a summary of a dialogue on screening activity by a focus group of community dentists organized in Vancouver late last year.[18] The goal of this initiative was to involve dentists directly in identifying barriers and facilitators to screening in community practices and to use this discourse to establish effective strategies for integrating screening into routine clinical practice. These same dentists are also serving as a pilot peer group that is exploring the use of new technology in the community to help set up protocols for effectively evaluating and transferring new technology into such settings.

Infrastructure organization and at least a degree of centralization are needed for any screening program to provide high-quality, cost-effective services. We recognize a need for continued growth and strengthening of the referral pathway.[2] Also important is the establishment of a screening registry, which will coordinate screening and diagnostic services and facilitate appropriate management and use of the referral pathway, avoiding unnecessary delays in diagnosis and treatment. Much of this activity is already evolving within the OBS. Creation of a central database within this structure will allow us to monitor program standards

regularly to identify areas for improvement. A screening program will be deemed effective only if quality criteria, including target figures and performance indicators, are set and achieved. As the program develops, expected outcomes include improvement in screening participation, changes in rates of detection from biopsies and decreased morbidity and mortality.

A further objective is to improve access to services by those not receiving regular dental care. This requires outreach involving new community partnerships and alternative strategies to reach high-risk, underserved populations, including the poor, immigrants, aboriginal people and the elderly. In British Columbia, for example, an outreach program at a dental clinic in the Downtown Eastside of Vancouver (Canada's poorest neighbourhood, with high levels of alcohol consumption and smoking) involves a partnership among the University of British Columbia, the Portland Hotel Society (a private society), the provincial government and the BC OCPP.[19] The program has identified the urgent need for dental and oral medicine care in such communities and has shown that the community is responsive to such initiatives and recognizes their value.

Looking Toward the Future: National and International Partnerships

The vision of the BC OCPP is to spread, share and disseminate technology and knowledge to the world to provide better care in oral cancer detection and management. Because two-thirds of oral cancers occur in developing countries,[1] this outreach will involve partnerships across cultures and between nations.

Our initiatives in British Columbia are "going global." For example, we have begun outreach in India, where oral cancer is one of the most prevalent cancers. Most cases of the disease occur in rural settings, where many people are poor and illiterate, many children and young adults are continuing to take up betel quid and tobacco chewing habits, and an epidemic of tobacco-induced cancers is predicted.[20,21] The challenge of controlling oral cancer in India is huge, but the impact will be great. To achieve this task, joint efforts and collaborations are being developed. The BC OCPP is committed to taking on this challenge and assuming a leadership role through partnership and transfer of technology and its modification to fit the needs of the intended setting. There are plans to extend this outreach to China.

In summary, this is a global disease. We need a global solution. So let us join hands and build partnerships. Together we can make a difference.

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Acknowledgments: *The authors acknowledge core support for this program, funding of the ongoing longitudinal study and ensuing technology development through grants R01 DE13124 and R01 DE17013 from the National Institute of Dental and Craniofacial Research/National Institutes of Health. The British Columbia Cancer Foundation has provided seed funding for community outreach. Dr. Poh is supported by a Clinician Scientist Award from the Canadian Institutes of Health Research and a Scholar Award from the Michael Smith Foundation for Health Research. We specifically thank the following people for their long-term support of our vision: Dr. Yasaman Shirazi, Dr. Simon Sutcliffe, Dr. Andy Coldman, Dr. Robert Priddy, Dr. Chris Zed, Dr. Kenneth Berean, Dr. Nhu Le, Dr. John Hay, Dr. Barry Sheehan, Dr. Janessa Laskin, Dr. Scott Durham, Dr. Don Anderson, Ms. Heather MacKay, Ms. Jocelyn Johnston and Dr. John O'Keefe. We are grateful to the many other members of the BC OCPP team and especially to the patients enrolled in the ongoing longitudinal study.*

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The authors have no declared financial interests.

This article has been peer reviewed.

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