



CHAPTER

69

*Prevention
of
Oral
Cancer*

By Carl Rosati

Prevention of Oral Cancer

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In 1979 the Canadian Task Force on the Periodic Health Examination identified cancers of the oral cavity as a potentially preventable cause of major morbidity and mortality. At the time, early detection was considered possible but the quality of evidence supporting the effectiveness of preventive strategies and the effectiveness of treatments for oral cancers was limited (C Recommendation). Review of the evidence from 1980 to 1993 has not changed this recommendation. However, smoking cessation counselling is highlighted as a means of preventing oral cancer and the recommendation to provide smoking cessation counselling is consistent with that made in Chapter 43 which deals more generally with the prevention of tobacco-caused disease.

Burden of Suffering



Oral cancers account for significant mortality but their prevalence is relatively low

The estimated incidence of oral cancers in Canada in 1993 was 3,120 and they accounted for 1,100 deaths, approximately 1.9% of all cancer deaths. The peak age for developing oral cancers is in the fifth to seventh decades with a male to female ratio of about 2.5:1. The lifetime probability of developing and dying from oral cancers in men is 1.71% and 0.61% and for women is 0.71% and 0.27%, respectively. The potential years of life lost (PYLL) for oral cancer was 16,000 years in Canada in 1989. Oral cancers account for significant mortality but their prevalence is relatively low. This may affect the feasibility of large scale screening with the adverse implications of the false positive and false negative diagnoses generated by such a screening program.

Over 50% of oral cancers, when diagnosed, are beyond the American Joint Committee for Cancer Staging and End Results' TNM Stage I. Consequently, there is major morbidity attributable both to the disease and to the various forms of treatment and all health status domains are affected. There is psychosocial disability in terms of appearance, self-esteem and withdrawal from familial and other social interactions. There are physical and functional disabilities in terms of personal hygiene, swallowing and maintenance of nutritional status, speaking and therapy-specific morbidities related to radical neck dissection and irradiation, thyroid and parathyroid dysfunction, mouth dryness from lack of normal secretion, osteonecrosis of facial bones and the adverse effects of chemotherapy.

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Cancer rates for both the salivary gland and nasopharynx are 10-25 times higher among the Inuit than among the general Canadian population; these cancers are associated with Epstein-Barr virus infection as well as genetic, environmental and immunologic factors. Alcohol and tobacco are major risk factors for tumours of the mouth, tongue and pharynx with a diet high in fresh fruits and vegetables acting as a protective factor. Smokeless tobacco use, including snuff and chewing tobacco is important (long-term users 50 times more likely to develop cancer of the cheek and gum than non-users) although vitamin deficiencies and occupational exposures are also implicated. Smokeless tobacco has other negative health effects<1> and in the United States use has increased over the last two decades largely due to increased consumption by young males. While smokeless tobacco use is rare in Canada (overall prevalence of use under 1% in 1986), prevalences of use of 6-30% among native children (depending on age and study population) and 1-4% among non-native adolescents have been reported.

Maneuver

There have been no randomized controlled trials to evaluate the effectiveness of oral cancer screening. In four studies, oral physical examination had a sensitivity of 59-100%, specificity of 95.9-99.7%, positive predictive value of 15-91% and negative predictive value of 99-100%;<2-5> positive predictive value is low. In addition to the psychological impact of labelling a patient with a false positive diagnosis, the added costs incurred by investigating patients so labelled would be prohibitively high. The principal reason for this problem is the low prevalence of oral cancers.

The use of toloum chloride testing in conjunction with oral physical examination should increase the recorded prevalence of oral cancer in case-finding (average sensitivity 96.7% with 90.8 average specificity), however Rosenberg *et al*<6> demonstrate that the prevalence remains sufficiently low to limit its usefulness. Several other issues such as reliability of the screening test, compliance with screening (affected by the misconception that asymptomatic lesions are innocuous), follow-up, definitive therapy and cost effectiveness should be considered for large-scale programs. No cost effectiveness study has been undertaken to determine whether the reduction in morbidity or lives saved through treatment of oral cancers at an early stage is sufficient to offset the cost of an oral cancer screening program.



There have been no randomized controlled trials to evaluate the effectiveness of oral cancer screening

Effectiveness of Prevention and Treatment

Risk Factors for the Development of Oral Cancers



There is good evidence from a meta-analysis of randomized controlled trials to recommend smoking cessation counselling

There is compelling evidence from case-control and cohort analytic studies, in varied geographic locations, of a causal relationship between the use of tobacco products, the combined use of tobacco and alcohol and the development of oral cancers.<7-16> Some of these studies demonstrated a reduction in the observed oral cancer rates with cessation of tobacco and/or alcohol consumption. There is good evidence from a meta-analysis of randomized controlled trials to recommend smoking cessation counselling (see Chapter 43 on Prevention of tobacco-caused disease).<17>

School-based programs to prevent smokeless tobacco use have had mixed results.<1,18-20> Evaluation of smokeless tobacco cessation programs has been limited, generally giving inconsistent results in small case series.<1> However, one randomized trial of 518 male smokeless tobacco users found that an intervention by dental hygienists (soft-tissue exam, advice to quit, self-help materials, video, quit date) improved quit rates at three months (32% of intervention group vs. 21% of controls, $p < 0.01$).<21>

Oral Premalignancy

A heterogeneous group of asymptomatic oral pathological entities with malignant potential includes dysplasia, erythroplasia, leukoplakia, lichen planus and submucosal fibrosis. The prevalence of oral premalignancy and its rate of malignant transformation are unknown. However, population-based studies from the U.S., Hungary, Sweden and India have estimated it to be 1.3% to over 6% and 2.2% to 6% respectively. Rates of malignant transformation of leukoplakia have been estimated at 2.2% to 6%. More recent prospective studies, with longer follow-up, and in populations with a higher proportion of dysplastic changes in their leukoplakias, suggest that the malignant transformation rates are higher than previously believed (16.2-17.5%). Although oral precancers are relatively infrequent and population screening may therefore be inappropriate, their relative importance and significant rate of malignant transformation would support case-finding strategies, particularly in high-risk populations. Arguments for adopting these strategies would be strengthened if supported by evidence of efficacious therapy for oral precancers.

Primary treatment of oral leukoplakia and therapy aimed at prevention of second primary lesions have been studied in two randomized, placebo controlled chemoprevention trials of 13-cis-retinoic acid (13cRA).<22,23> These studies demonstrated a reduction in relative risk to almost 1.0 for the complete remission of leukoplakia and a 0.83 relative risk for the occurrence of second

primary oral cancers suggesting that 13cRA was highly efficacious for these purposes. However, leukoplakia relapsed within 3 to 6 months after discontinuation of therapy, the rate of mild to moderate side effects was up to 79%, dose reduction was required in 18% to 47% of patients and at least temporary cessation of therapy was required in 4.5-6.8% of patients. Furthermore, an issue not addressed by the advocates of 13cRA was the teratogenicity of retinoic acid. Results of preliminary trials of low-dose maintenance therapy using 13cRA are encouraging, though follow-up to date is limited.<24>

Trials using β -carotene demonstrated reductions (up to 71%) in the occurrence of oral leukoplakia and mucosal dysplasia to a much lesser degree than that observed with 13cRA.<24-27> Adverse effects were virtually nonexistent. Current research on low dose maintenance and alternative (β -carotene) therapies may soon resolve these issues.

Effectiveness of Treatment of Invasive Oral Cancers

The choice of therapy for early stage invasive oral cancer is controversial. Primary surgical and radiation therapy are often considered equivalent. While opinion varies considerably, particularly concerning the adverse effects of both forms of therapy and their impact on quality of life, there appears to be no difference in survival between these therapies based on the current evidence in the literature.

Multivariate analyses, in studies of both surgical and radiation therapy, have consistently identified the stage of disease as an important prognostic factor. The 1991 American Cancer Society's national five-year survival figures for oral cancer based on stage were, Local 75%, Regional 41% and Distant 18%.<23> Similar five-year survival statistics are provided in a review of the literature specifically addressing treatment of oral malignancies: Stage I 68-89%, Stage II 40-83%, Stage III 29-68%, Stage IV 6-36%.<23,28-35> These data suggest that there is a survival difference depending on the stage of the disease at the time of diagnosis but do not address lead-time or length-time bias. Two retrospective cohort studies report survival beyond five years.<23,28> Survival figures at 10 years demonstrate an increase in oral cancer-specific mortality raising concerns over lead-time bias. A single randomized controlled trial comparing elective versus therapeutic neck dissection for oral cavity carcinoma demonstrated an overall 70% survival rate for both groups at six years follow-up.<36> However the authors reported their results for all stages (I, II, III) combined. Thus, while lead-time bias may not have been an issue, it is not possible to determine the effect of treatment on early stage disease. Several large case series report similar five-year survival figures and identify second primary oral cancers as the leading cause of death in these patients after local or regional recurrence.<29-33,36>

The rates of second primary oral cancers exceeds 36% and adds further to the confusion in interpreting the effectiveness of treatment for invasive oral cancers. Definitive conclusions regarding both the most effective form of therapy and the effectiveness of treatment for early stage oral cancers await a prospective randomized trial.

Recommendations of Others

In 1989, the U.S. Preventive Services Task Force recommended counselling patients against the use of tobacco in any form, particularly with heavy alcohol consumption, based on evidence linking the adverse effects of tobacco with premalignant and malignant lesions of the oral cavity.<37> Routine screening of asymptomatic persons for oral cancer by primary care clinicians was not recommended. However, it was thought to be prudent for clinicians to perform careful examinations for cancerous lesions of the oral cavity in patients who use tobacco or excessive amounts of alcohol, as well as in those with suspicious symptoms or lesions detected through self-examination. These recommendations are currently being reviewed.

The Canadian and American Dental Associations support the concept of oral cancer screening; however, neither group has recommended specific clinical practice guidelines in this regard.<38-43>

Conclusions and Recommendations

Ample evidence establishes the causal link between use of tobacco products in any form and cancers of the aerodigestive tract, based on extensive case-control and cohort studies. In addition, there is good evidence supporting the effectiveness of counselling for smoking cessation. There is good evidence to include smoking cessation counselling in the periodic health examination to prevent oral cancer (A Recommendation).

There is insufficient evidence, however, for inclusion or exclusion of oral cancer screening in a periodic health examination (C Recommendation). Annual examination by physicians and/or dentists should be considered for men and women over 60 years of age who have known risk factors for oral pre-malignancy and invasive oral cancers, such as tobacco use in any form and regular alcohol consumption. Individual judgement should be exercised regarding the use of toloum chloride for those identified by positive oral physical examination and referral to a specialist for further diagnostic evaluation.

Fair evidence exists supporting the efficacy of 13cRA in the treatment of oral leukoplakia; however, the high recurrence rates following cessation of therapy and the high rate of adverse effects limit

its potential usefulness. Therapy with these agents remains investigational.

Unanswered Questions (Research Agenda)

Further prospective studies are required to strengthen the evidence demonstrating the effectiveness of primary prevention strategies.

Further research should be directed to determining whether current treatment modalities are in fact effective in a well designed randomized controlled trial. Once this is established then efforts to determine the reliability, validity and responsiveness of the most effective screening or case-finding maneuvers may be undertaken. Furthermore, there is evidence to suggest that screening by oral physical examination may be performed by different disciplines, using simple maneuvers. A cost effectiveness study of such a screening program is required to determine the most feasible screening strategy.

Evidence

The literature was identified with a MEDLINE search for the years 1980 to 1993, limited to studies in the English language. The following key words were used: mouth neoplasms, health status indicators, population surveillance, mass screening combined with evaluation studies, outcome and process assessment, mortality and prognosis.

This review was initiated in January 1993, and the recommendations were finalized by the Task Force in June, 1993.

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**Prevention of Oral Cancer**

MANEUVER	EFFECTIVENESS	LEVEL OF EVIDENCE <REF>	RECOMMENDATION
Smoking cessation counselling	Use of multiple intervention and reinforcement strategies increased 6-month and 1-year cessation rates.	Randomized controlled trials<17> (I)	Good evidence to include in periodic health exam (A)
Screening by oral physical examination	<p>Low prevalence of oral cancers and poor positive predictive value of physical exam (even in conjunction with use of tolonium chloride testing) limit usefulness. Potential for labelling, cost of follow-up and marginal benefits demonstrated for therapy are additional considerations.</p> <p>Use of 13-cis-retinoic acid (13cRA) reverses or stabilizes premalignant lesions and reduces the rate of second primary malignancies. Side effects, potential teratogenicity and relapse after discontinuation limit usefulness. B-carotene reduces occurrence of oral leukoplakia and mucosal dysplasia to a lesser degree than 13cRA, without side effects.</p> <p>Survival of patients with invasive cancer appears comparable for surgical and radiation therapy; earlier stage of disease is an important prognostic factor.</p>	<p>Cohort and case-control studies<2-6> (II-2)</p> <p>Randomized controlled trials<22-27> (I)</p> <p>Cohort studies<23,28> (II-2); case series <29-33,36> (III)</p>	<p>Insufficient evidence to include or exclude from periodic health exam (C); annual examination by physician and/or dentist should be considered for men and women over age 60 years with risk factors for oral cancers and precancers; individual judgement should be exercised regarding the use of tolonium chloride for those identified as positive by oral physical exam</p>