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Published

2011

Journal Title

Advances in Dental Research

DOI

10.1177/0022034511402082

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Global Inequalities in Incidence and Outcomes for Oral Cancer: Causes and Solutions

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Adv Dent Res X(X):xx-xx, XXXX

ABSTRACT

The mouth and oropharynx are among the ten most common sites affected by cancer worldwide, but global incidence varies widely. Five-year survival rates exceed 50% in only the best treatment centers. Causes are predominantly lifestyle-related: Tobacco, areca nut, alcohol, poor diet, viral infections, and pollution are all important etiological factors. Oral cancer is a disease of the poor and dispossessed, and reducing social inequalities requires national policies co-ordinated with wider health and social initiatives – the common risk factor approach: control of the environment; safe water; adequate food; public and professional education about early signs and symptoms; early diagnosis and intervention; evidence-based treatments appropriate to available resources; and thoughtful rehabilitation and palliative care. Reductions in inequalities, both within and between countries, are more likely to accrue from the application of existing knowledge in a whole-of-society approach. Basic research aimed at determining individual predisposition and acquired genetic determinants of carcinogenesis and tumor progression, thus allowing for targeted therapies, should be pursued opportunistically.

DOI: 10.1177/0022034511402082

INTRODUCTION

Modus Operandi

This report describes inequalities between and within nations in incidence, mortality, risk factors, and provision of care; it suggests causes for these inequalities/disparities, identifies gaps in knowledge, and poses research questions. The WHO Global Commission on Social Determinants of Health states that: *[Health inequalities are] "caused by the unequal distribution of power, income, goods and services, globally and nationally, the consequent unfairness…in access to health care, schools, education, conditions of work and leisure, homes, communities,… and chances of leading a flourishing life…. Poor and unequal living conditions are the consequence of poor social policies and programmes, unfair social arrangements and bad politics."* (CSDH, 2008) Oral health is no different (Petersen, 2009; Sheiham *et al*., 2011), and contributory causes include social determinants (Marmot, 2010), socio-economic disadvantage, and the gradients both within (Wilkinson and Pickett, 2010) and between countries. The needs are for clean air and water, food security, an affordable and healthy diet, good hygiene, and freedom from pestilence and war.

Definitions of Oral Cancer and Epidemiology

Globally, over 90% of malignancies affecting the mouth and maxillofacial region are squamous cell carcinomas (SCC). In sub-Saharan Africa, AIDS-associated Kaposi sarcoma remains common, and odontogenic neoplasms are prevalent in many developing nations. Though more rare, bone and soft-tissue sarcomas have high morbidity and mortality; malignant salivary tumors and lymphomas contribute to the burden. [For fuller coverage of epidemiology, see Johnson and Amarasinghe (2011) and Johnson *et al*. (2011).] Fig. 1 ranks the 15 most common cancer sites. If other upper-aero-digestive tract (UADT) sites with common risk factors (oro-/hypo-pharynx and larynx) are added to lip/oral, these malignancies always rank in the top ten (Ferlay *et al*., 2010b), and in some countries oral cancer is the most common (*e.g.,* Tamil women in Malaysia and men in Sri Lanka).

Key Words

Oral carcinogenesis, access to care, treatment planning.

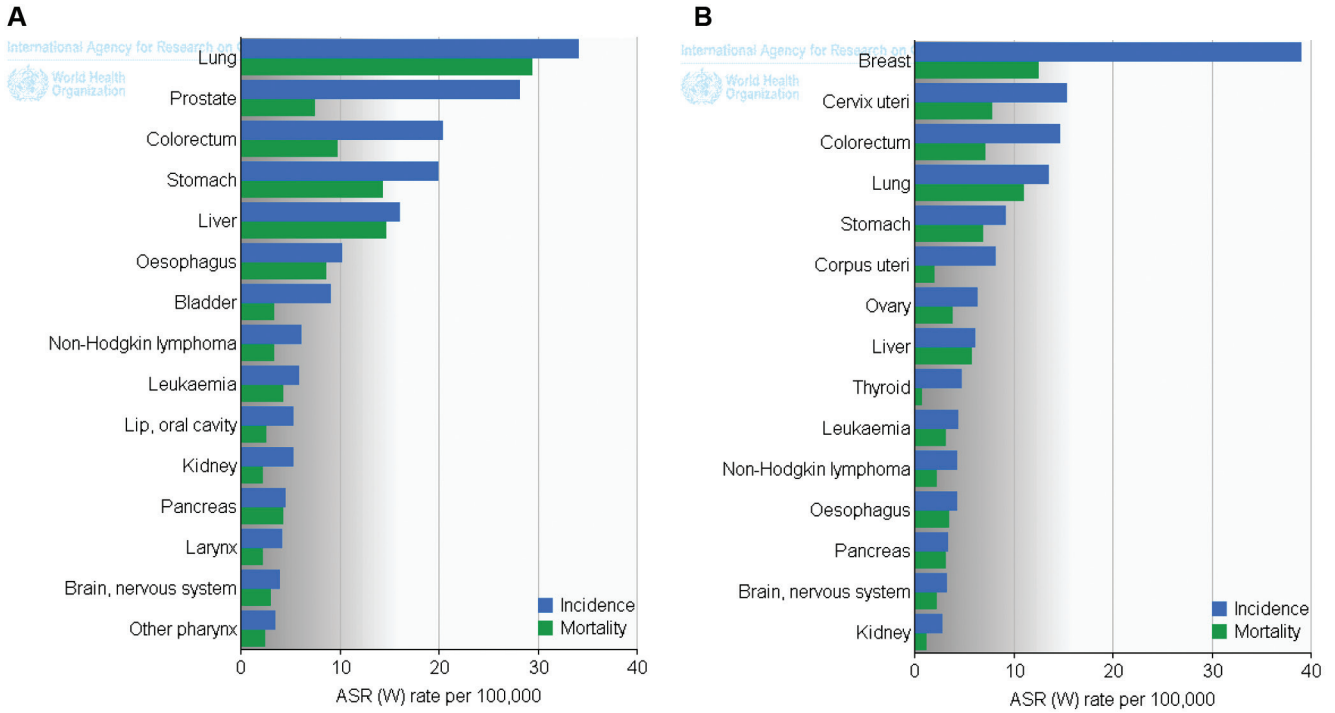

Fig. 1. The most common sites/types of malignant neoplasms, global summary. **(A)** Male. **(B)** Female.

Geographical patterns of oral cancers (Globocan, 2008; Fig. 2) are indicative of differences in risk factors, particularly tobacco, areca, and alcohol consumption, and quality of diet. Two-thirds of these malignancies occur in developing countries.

The highest incidence of lip/oral cancer is in Melanesia (Papua-New-Guinea [PNG]: 32.3/100,000 reported annually in men and 16 in women, standardized to the world population [ASRW]), associated with chewing of areca nut and tobacco use. In India, over 100,000 cases are registered annually. Though men predominate overall, a very high incidence is found among females throughout Southern Asian (8.3/100,000 annually). Sri Lankan males have the highest incidence of oral cancer in South Asia (16.5/100,000). In Taiwan, male incidence (ASRW) for lip/oral cancer is 29.2/100,000 annually.

Most cases occur in the fifth to seventh decades of life, probably because long exposure to tobacco, alcohol, and poor nutrition is needed for interaction with other agents to trigger malignant transformation. All UADT cancers show similar age distributions. A significant minority appears in the fourth-fifth decades, and these attract interest. Although early commencement of smoking and unsafe alcohol use can be demonstrated, a substantial minority of cases arises in the absence of traditional risk factors (Llewellyn *et al*., 2004).

In the high-incidence age bands, there is a ~ 40- to 100-fold difference in incidence, with disturbingly high rates in NW France, Hungary, Brazil, and India. The situation is much worse in American blacks than whites, for risk factor and socio-economic reasons.

DIFFERENCES IN MORTALITY BY REGION AND COUNTRY

Traditionally, high-incidence areas of central Asia and the Indian subcontinent stand out (Fig. 3). Much is due to betel quid, with or without smokeless tobacco, smoking, sometimes alcohol, and poor diet. Importantly, parts of both Western and Eastern Europe remain in the top quintile.

Australia has a high incidence, due to ultraviolet-light-induced lip cancer in a fair-skinned population, but with low mortality rates, because this is easily treated. Eastern Europe and the former Soviet republics have high mortality because of limited treatment facilities and co-morbidities. PNG and the surrounding Melanesian islands are in the top quintile in both incidence and mortality.

Differences in Incidence and Mortality within Western Industrialized Countries

These apparently relate to regional differences in risk factors. The historically high rates in Northwestern France, now coming under control, and the still-growing rates in central and eastern Europe (Ferlay *et al*., 2010a) are associated with heavy tobacco and alcohol use – the latter involving acetaldehyde-containing fruit distillates.

Socio-economic Status (SES)

There is a marked association between oral cancer and SES (Hobdell *et al*., 2003; Warnakulasuriya, 2009a). A Brazilian

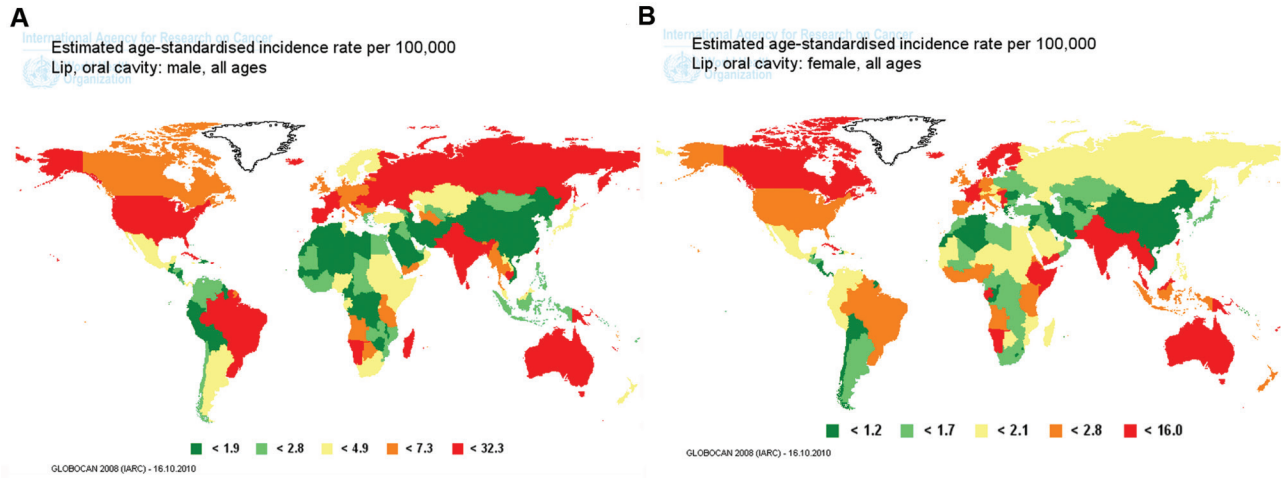

Fig. 2. Incidence rates for lip and oral cavity cancer, by country, from highest quintile (red) to lowest (green). **(A)** Male. **(B)** Female.

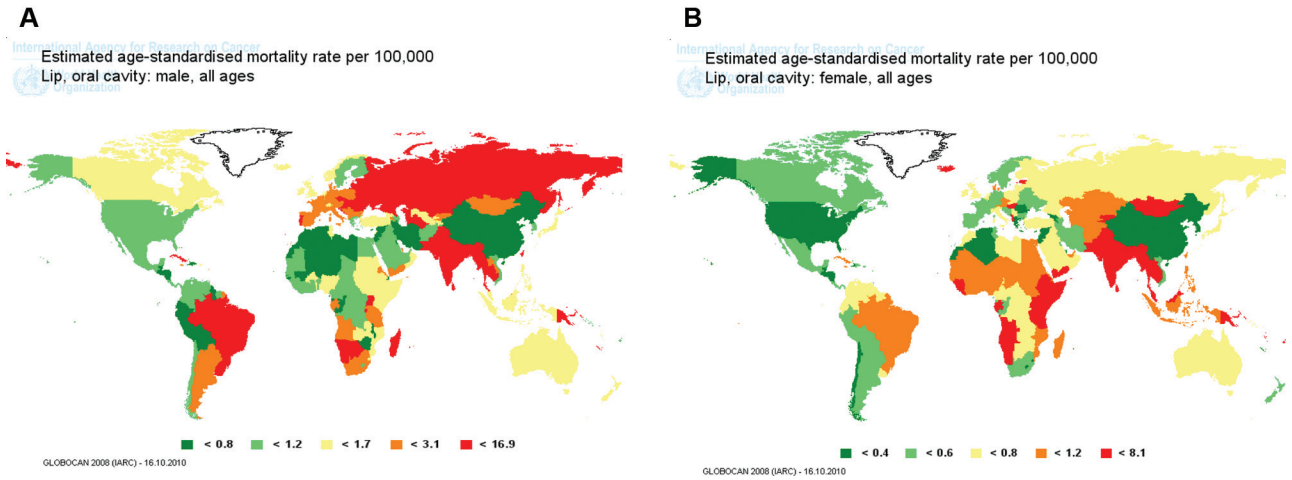

Fig. 3. Global mortality from oral cancer. **(A)** Male. **(B)** Female.

case:control study has determined that about half the elevated risk for head and neck cancer associated with low SES (OR 2.2 for low education; 1.55 for manual laborers) is explained by alcohol and tobacco (Boing *et al*., 2009). Diet and hygiene might largely explain the remainder.

ORAL POTENTIALLY MALIGNANT DISORDERS (OPMD)

In the West, most cases of SCC arise with neither the patient nor the managing clinician being aware of any pre-existing lesion/condition, despite a likely background of systemic predisposing factors and regional molecular lesions. OPMD precede most cases of SCC in Asia, providing opportunities for early intervention: on a population basis, as screening targets and triggers for health promotion; and on a patient basis, for habit intervention, nutritional support, and surveillance for malignant transformation. There is no evidence of benefits from such interventions, and there is a need for research into effects on natural history and outcomes.

Priorities for Action

- Effective cancer registration in all countries, in collaboration with authorities like the International Prevention Research Institute (iPRI, Lyon, France), the International Agency for Research on Cancer in Lyon (IARC, a WHO Agency), and/or Centers for Disease Control and Prevention (CDC) in the USA. Reliable data are fundamental to allowing etiological factors to be determined and trends in incidence and treatment efficacy to be monitored.
- Registries are needed for OPMD to facilitate studies on natural history, including systemic, clinical, histological, and whole-genome tracking of molecular abnormalities, and on the efficacy of habit interventions and of treatments (surgical, chemopreventive, and chemotherapeutic). The international

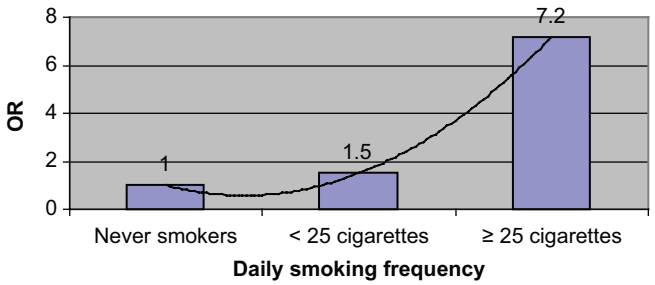

Fig. 4. Odds ratios for oral and pharyngeal cancer in non-drinkers (Talamini *et al.*, 1998).[AQ: 15]

network of registries, including the Union Internationale Contre le Cancer (UICC), iPRI, IARC, CDC, NIH National Cancer Institute, and NIDCR, should be enlisted.

IMPORTANT RISK FACTORS FOR ORAL CANCER AND APPROACHES TO PRIMARY PREVENTION

Tobacco

Nearly 1.3 billion adults > = 15 years of age smoke daily [~ 29% of adults: 48% of men, 10% of women worldwide (Guindon and Boisclaire, 2003)], and 5.4 million people die annually from smoking-related diseases, rising to 8 million by 2030, with a clear social gradient. Tobacco use is the single most important risk factor for oral cancer; a meta-analysis has determined the relative risk (RR) for oral cancer in current smokers to be 3.43 (95% CI: 2.37–4.94) (Gandini *et al*., 2008), and this is dose-dependent (Fig. 4).

Most countries have neither tobacco legislation nor health warnings, and enforcement is poor even where laws exist. Only 9 out of 73 WHO member states offer the highest level of support for cessation, and only 2% of the world's population is protected by adequate taxation on tobacco. Governments around the world collect more than US$ 200 billion in tobacco taxes each year, but spend less than 1% of that amount on tobacco control (WHO, 2008).

Smokeless tobacco use is increasing, partly due to policies prohibiting smoking in public and claims by manufacturers that it is safer.

All countries should do more to contain the tobacco epidemic, and reasons for failure to implement effective control measures require analysis (Jha *et al*., 2006; Davis *et al*., 2007; WHO, 2008; Owusu-Dabo *et al*., 2010). The key message must be: "Through the mouth you can bring health, or disease and death – please choose health."

Gaps in Knowledge

- Information on tobacco use is inadequate for over half the world's population. Low-/middle-income countries have weak monitoring systems. The Global Adult Tobacco Survey and the WHO STEPS, plus the Global Youth Tobacco Survey, may improve the situation.
- Awareness among political leaderships about the burden of disease due to tobacco and the benefits of adopting tobacco control policies for their own political security is inadequate.
- A significant proportion of dental practitioners and students in different countries smoke or use other forms of tobacco, and their preparedness to counsel tobacco users for cessation is inadequate
- We do not know the extent to which young people value good oral hygiene and would quit tobacco use if they understood the health and social benefits of oral hygiene and the harmfulness of tobacco.

Research Agenda

- Involve professional dental associations in advocacy and informing political leaders about expected benefits of tobacco control. This is a key opportunity for joint working with the FDI.
- Improve existing dental health services for children and youth; promote brief interventions on tobacco, alcohol, and recreational drugs through these services; measure their efficacy.
- Test the effectiveness of delivering dental care and tobacco-cessation counseling as an integral part of health services in developing countries. Measure impact on disease.
- Test the effectiveness of involving youth in advocacy for tobacco control, as in India.
- Test educational interventions among teenagers in schools and communities on the benefits of oral hygiene, proper diet and exercise, and harms of tobacco and alcohol use.

Funding sources for tobacco control research are available (Lando *et al*., 2005)

Areca Nut, Betel Quid, Pan Masala, Gutka

Betel quid with or without chewing tobacco is common in South Asia. It contains leaves of the *Piper betel* vine, smeared with lime paste (aqueous calcium hydroxide), chopped nuts of the *Areca catechu* palm (*Chrysalidocarpus lutescens*) tree, and condiments including astringent catechu bark extract (*Acacia catechu*), cardamom, clove, and sweeteners. In South/SE Asia, it is mainly consumed with tobacco; in China and Taiwan, it is mainly chewed by itself, though most users smoke cigarettes. In South Asia, there has been a recent, major increase in pan masala and gutka consumption (Gupta and Warnakulasuriya, 2002). These recent, commercialized, dry-packaged versions of betel quid do not include betel leaves. They are mainly produced in India and exported to over 30 countries.

Areca nut alone is formally recognized by the IARC as carcinogenic; the dangers are much enhanced if tobacco is included (Secretan *et al*., 2009). It is highly addictive. The ORs for oral cancer are summarized in Fig. 5. Betel quid is the major risk factor for OPMD and oral cancer in Sri Lanka, a fact of which the population is largely unaware (Amarasinghe *et al*., 2010a,b).

Research Agenda

- Culturally sensitive health education promotion programs against areca/smokeless tobacco should be introduced and

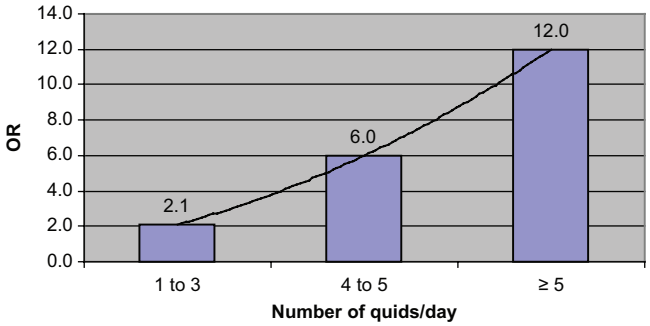

Fig. 5. Odds ratios for oral cancer in chewers - mainly of betel quid; adjusted for alcohol (Znaor *et al.*, 2003).

evaluated in multiple settings, targeted to high-risk groups, especially women.

- Coordinated planning and implementation are required, involving oral/dental scientists, epidemiologists and public health professionals, behavioral scientists, governments, and non-governmental organizations (NGOs). Oral health promotion messages– including prevention of oral cancer – should be embedded into a common risk factor approach. The dental professions will not succeed in isolation.

Marijuana

Chronic smoking of marijuana carries risks comparable with those of tobacco smoking for UADT cancer. Additional challenges for preventive strategies arise because of the particular communities and individuals who are habituated (Cho *et al*., 2005).

Alcohol Abuse

Alcohol is one of ten leading risk factors of disease: 4% of the global disease burden is attributed to its use. It is linked to 60 diseases, nine causally, and numerous social problems. It is a particular factor for oro-pharyngeal cancer (OPC). Global *per capita* consumption has increased in recent decades, associated with urbanization and industrialization, and is accompanied by increased tobacco use, shifts toward refined diets, and lower physical activity. In combination with smoking, it increases the risk of OPC super-multiplicatively (Secretan *et al*., 2009; Goldstein *et al*., 2010).). A meta-analysis of 26 European studies found strong direct trends (Fig. 6). For consumption of 25 g *per* day, the RR adjusted for smoking was 1.76 (1.69-1.82), for 50 g/day, 2.87 (2.68-3.08), and for 100 g/day, 6.10 (5.45-6.83). A dose-response relationship is clear, and the risks are greater than those for tobacco alone. The dominant type of alcohol consumed is associated with greatest risk.

Gaps in knowledge include the levels of policy enforcement in each country and the lag-time between implementation of a control and its effect. The effectiveness of messages about oral health risks due to alcohol has not been measured. Brief interventions in dental practice to motivate people to reduce consumption of alcohol have not been well-studied.

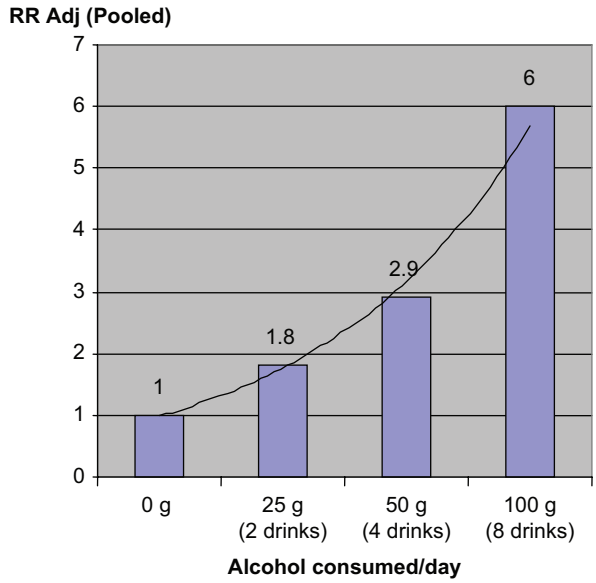

Fig. 6. Odds ratios for oral and pharyngeal cancer by alcohol consumption (Bagnardi *et al.*, 2001).

Research Agenda

- *Advocacy Research for Alcohol Control*. Document levels of enforcement for current policies. Test different strategies for generating commitment of politicians/governments toward stronger policies. Promote an international treaty on alcohol control. Work on increasing taxation/prices to reduce consumption and discourage smuggling.
- *Communications Research*. Test different methods for reaching youth target-groups with alcohol control messages, including messages on oral health. Measure retention of messages, self-reported alcohol use, and emergence of youth leaders in alcohol control.
- *Clinical Research: Brief Interventions; Workplace Support Groups*. Test the efficacy of different brief interventions in dental/medical settings on reducing alcohol abuse and oral disease.
- *Social Research on Prevention of Alcohol Abuse in Communities at Risk*. Test the efficacy of targeting at-risk groups for prevention of alcohol abuse with health messages, literacy, basic education, and skills training aimed at helping them gain control over their lives.

The above should be combined with tobacco control, diet counseling, and sexual hygiene in a multi-sectoral approach. The oral health community should not work in isolation.

Poor Nutrition

Two-thirds of the world's oral cancers are reported from South Asia and the Pacific, where GNP is low and food energy is either low or acquired from starchy foods. SES, an established risk factor for oral cancer (Conway *et al*., 2008), is a surrogate marker for poor nutrition. Low BMI enhances smoking- and drinking-related ORs for OPCs (Lubin *et al*., 2010).

ARs [AQ: 1]of cancer from poor diet are ~25% (Doll and Peto, 1981). UADT cancers can be prevented by diets rich in anti-oxidants, notably fresh fruits and vegetables. Dietary goals set by the World Cancer Research Fund (WCRF, 2007) are based on credible data. Under-nutrition is a major factor in the gap between poor and rich countries and within countries. Acceptance of the potential for oral cancer reduction through improved diet represents a remarkable paradigm shift.

Increased consumption of green leafy vegetables and non-starchy tubers, *e.g.,* carrots, reduces the risk of OPC (Pavia *et al*., 2006; Warnakulasuriya, 2009b). Fruits, particularly citrus, have an even greater protective effect against UADT cancers than do vegetables. Mediterranean-style diets rich in carbohydrates, vegetable oil, fish, fruits, and vegetables, and poor in meat and animal fat, contribute to health (IARC, 2008; Samoli *et al*., 2010).

Iron deficiency is widespread in developing countries, and resultant mucosal atrophy may predispose to oral cancer (Warnakulasuriya and Prabhu, 1992). Poor diet may favor progression of OPMD to cancer; deficiency of β carotene is a risk factor for oral leukoplakia (Nagao *et al*., 2000), whereas micronutrient supplementation is helpful in the management of oral submucous fibrosis (Maher *et al*., 1997).

Chemoprevention is the attempt to reduce cancer incidence by prescribing relevant bioactive substances, but the effectiveness of this approach in reversing potentially malignant disorders remains unproven. Even where improvements are noted, recurrence often follows (O'Shaughnessy *et al*., 2002). Further multicenter randomized controlled trials (RCTs) of dietary supplementation for persons with OPMD are required to assess the efficacy of vitamins, retinoids, or carotenoids (Scheer *et al*., 2004).

Gaps in knowledge include information on dose-responses for quantities of fruits, vegetables, and combination diets that help in prevention, the utility of biomarkers, and RCTs on chemoprevention among low-SES communities.

Priorities for Action to Reduce Inequalities

- Work effectively with other agencies to improve access to secure and nutritious foods for all.
- Quality multidisciplinary/multicenter RCTs to evaluate chemoprevention of oral cancer, particularly transformation of OPMD. Collaboration with major international bodies is essential.

Human Papillomaviruses

Infection with high-risk HPVs, genotypes 16 and 18, is an independent risk factor or partial cause of oral cancer, particularly of the oropharynx and posterior tongue. This may be particularly relevant in younger people, where sexual transmission is implicated. ARs [AQ: 2]are likely to vary both between and within countries in relation to social habits and the overpowering effects of tobacco, alcohol, and diet.

A meta-analysis of 1121 published studies of oral lesions (Syrjänen *et al*., 2011) reported ORs for association with high risk HPVs and oral cancer at 4.0 (2.62 – 6.02), and at 4.1 (2.3-7.7) for OPMD.

In the West, the rise of OPC among the young more than offsets the decline in tobacco- and alcohol-related cancers; nevertheless, in all cases, tobacco use affects outcomes adversely. HPV-related cancer has a better prognosis than cancer in older individuals (Ang *et al*., 2010).

Priorities for Research

- Trends in incidence of OPC in young people should be carefully monitored.
- Detection of HPV should be part of the assessment of OPC patients. This requires robust, cost-effective tools suitable for resource-poor settings. Basic research is required on methods.
- Formal links should be established with governments and pharmaceutical companies engaged in HPV vaccine trials for the prevention of cervical cancer, to establish the impact on OPC.
- Health promotion activities directed against oral cancer should include sexual hygiene and must be culturally sensitive.

Common Oral Diseases and Oral Hygiene/Mouthwashes

Several case:control studies have sought to assess the risk of poor oral hygiene, tooth loss, or periodontal disease in terms of risk of OPC (Guha *et al*., 2007). This is related to suggestions that frequent use of alcohol-containing mouthwashes contributes to oral cancer. Most studies alluding to such risks are based on patient recall of oral hygiene practices and on self-reported "dental status".

There is biological plausibility for a role for high levels of oral biofilm with its associated ecological shift to a more toxic microflora, including enhanced synthesis of acetaldehyde from alcohol in the mouth. However, a recent meta-analysis of published epidemiological studies found no significant risk.

Priorities for Research

- Case:control studies, involving multidisciplinary teams with full oral examination of the study population, to quantify oral disease history. Both OPMD and OPC cases should be included.
- These studies should include intervention arms designed to test health promotion activities.

Indoor Smoke

Indoor air pollution contributes to UADT malignancy, with other significant inflammatory respiratory diseases and infections (IARC, 2006). This is a particular problem in rural Africa and Asia.

Priorities for Action

- Greater awareness among governments, professions, and public of this issue.
- Linkage with local initiatives and global aid programs that aim to improve access to clean water, nutritious foods, and healthy living environments, including cooking facilities.

Industrial Pollution

Those living in proximity to, or working at, industrial plants handling hydrocarbons or cement are at increased risk of UADT cancer.

Priorities for Action

- Greater awareness among governments, the professions, and the public of this issue.
- Linkages as above.
- Improved epidemiological data from detailed case:control studies.

SECONDARY PREVENTION – SCREENING PROGRAMS

The main goals of oral cancer screening are preventing deaths and improving quality of life cost-effectively. Thus, OPC must be identified in the pre-clinical phase with biologically significant disease; treatment must be more effective in the pre-clinical than the symptomatic phase and must reduce the death rate; and the screening test must be affordable and safe, with high sensitivity and specificity and low false-positive rates. Target populations for oral cancer screening are those aged > = 35 years who use tobacco or alcohol. In low-incidence countries such as England, population screening for oral cancer is not recommended (Speight and Warnakulasuriya, 2009), but it has been shown to be effective in Kerala, India.

Oral cancer screening programs include (Rethman *et al*., 2010):

- Oral visual screening
- Mouth self-examination
- Adjuncts to visual screening
  - Toluidine blue intravital staining
  - Chemiluminescence (ViziLight™, MicroLuX DL™, Orascoptic DK™, etc.)
  - Autofluorescence (VELscope™)
  - Autofluorescence spectroscopy
- Exfoliative cytology (OralCDxBrush Test™)
- Saliva analysis

The sensitivity of oral inspection in detecting OPMDs and OPC varies from 40-93%, and the specificity ranges between 50 and 99%, indicating that it is a suitable screening test. The positive predictive value for OPMDs and oral cancer ranges from 2-20%, depending upon prevalence of lesions, sensitivity of the test, and competency of the provider. Potential harms include: additional investigations, *e.g.,* biopsy; unnecessary treatment of non-progressive OPMDs; anxiety associated with false-positive tests; and false reassurance from false-negative tests. Educational resources are available (*e.g.,* http://screening.iarc.fr/atlasoral.php).

Adjunctive Tests

The reported accuracy cannot be extrapolated to whole populations, since studies are based on small case-series with a high prevalence of lesions. Evaluation of their feasibility, clinical utility as triaging tests, cost-effectiveness, and effectiveness in reducing oral cancer mortality requires large-scale population-based studies.

Effectiveness of Oral Cancer Screening

An RCT is the proper means of evaluating whether a screening test reduces disease-specific deaths. Individuals aged 35 years and above in 13 clusters in Kerala, India, were randomized to receive three rounds of oral visual inspection at three-year intervals by trained health workers (7 clusters, 96,517 individuals), with controls (6 clusters, 95,536 individuals). In all, 33,343 individuals received a single screen, 24,210 two screens, and 29,102 three screens. In the intervention group, 87,645 (91%) of eligible individuals were screened at least once: Overall, 5145 were screen-positive, of whom 3218 (63%) complied with referral. Deaths were lower in the intervention group: 77 oral cancer deaths compared with 87 in controls - a mortality ratio of 0.79 (95%CI: 0.51-1.22). As expected, 96% of all oral cancer cases occurred among users of tobacco, alcohol, or both, so mortality rates among these high-risk subjects were compared. There were 70 oral cancer deaths among 45,651 individuals with tobacco and alcohol habits in the intervention group, with 85 among 38,539 such persons in the control group: a mortality rate ratio of 0.66 (95% CI: 0.45-0.95). This significant 34% reduction in oral cancer mortality among users of tobacco or alcohol in the intervention group, compared with the control group, clearly established that oral visual screening could reduce oral-cancer-specific mortality among people at risk. Screening cost under US$6 *per* person; the incremental cost *per* life-year saved was US$835 for all individuals eligible for screening and US$156 for users of tobacco or alcohol. Thus, the most cost-effective approach to oral cancer screening by visual inspection is to offer it to users of tobacco, alcohol, or areca (Subramanian *et al*., 2009; Amarasinghe *et al*., 2010a,b).

Oral self-examination by means of a mirror has been evaluated as a screening test in some studies, but its impact on mortality is unknown.

Priorities for Research

- Evaluate performance and cost-effectiveness of adjunctive tests in cross-sectional and longitudinal studies.
- Evaluate salivary analysis both for primary screening and as a diagnostic procedure.
- Determine malignant transformation rates of well-categorized OPMDs in population-based longitudinal studies.
- Identify and evaluate potential genetic and other biomarkers that predict natural history and prognosis of OPMDs.
- Determine the long-term outcomes of treatment of OPMDs.
- Determine the factors that predict and improve the participation of target populations in oral cancer screening.
- Evaluate the effects of improving awareness of oral cancer on prevention and early detection among the general population and health care providers.
- Determine the reasons for late presentation of oral cancers and delays in treatment.

- Document the performance of ongoing national oral cancer screening programs.
- Document trends in stage-specific incidence rates of oral cancer in population-based cancer registries and correlate these with ongoing opportunistic and organized oral cancer screening initiatives.
- Document the harms and long-term sequelae of screening and quality-of-life issues in such programs.
- Evaluate online and digital learning resources for oral cancer screening using in-service training of health care providers in routine health services.

ACCESS TO CARE: TERTIARY PREVENTION

Long-term survival and quality of life after diagnosis of oral cancer depend most on the clinical stage at presentation and access to evidence-based multidisciplinary treatment. This is unrealistic for most of the developing world, because health education and screening are virtually non-existent in these areas, and most patients present with advanced tumors (Carvalho *et al*., 2002). Delay in presentation is attributed to lack of awareness of early symptoms and access to health systems. Professional delay is related to failure of primary care professionals to recognize signs and symptoms indicative of cancer. The main factors associated with late presentation and diagnosis are gender, dental status, alcohol consumption, SES, and tumor location, especially at less visible surfaces of the oral cavity (Carvalho *et al*., 2002).

Treatment of oral cancer should be initiated quickly, but access to centers providing multidisciplinary treatment is limited in developing countries. Facilities for sophisticated reconstruction, advanced radiotherapy, and medical oncology are rare. The high cost of modern cancer care is unaffordable in health systems with low resources, and high demand on facilities leads to delay, contributing to upstaging of disease and decreased survival (Kowalski and Carvalho, 2001).

Priorities for Action

- Improving early diagnosis through public health education programs on risk factors and early signs and symptoms.
- Effective continuous education programs on diagnosis of OPMDs and early cancer for all primary care providers.
- Create comprehensive head and neck cancer databases in every treatment institution.
- Implementation of multidisciplinary approach as recommended by, for example, the British Association of Head and Neck Oncologists and the American Head and Neck Society.
- Development of treatment guidelines for developing countries, including survival, quality-of-life, and cost considerations.
- Training programs in surgery and oncology for young clinicians in developing countries.
- Continuing medical education for surgeons and oncologists in developing countries.

SPECIAL CHALLENGES OF RESOURCE-POOR REGIONS

Most developing regions have ethnic diversity and environments with a largely unquantified impact on disease burden, morbidity, and mortality from OPC. Community- or population-based databases are inadequate, and there is persistent failure to develop evidence-based alternatives to current management strategies, despite oral cancer being a top priority of the WHO/AFRO Regional Oral Health Strategy (1998-2008). Accurate population surveillance, good clinico-pathological diagnostics, better treatment facilities, and targeted basic research are needed.

Priorities for Action

- Comprehensive, evidence-based national cancer control programs can improve the lives of patients in developing regions, but these require coordination with established campaigns against infectious diseases. This approach can work (Farmer *et al*., 2010).
- Liaison with the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries (GTF. CCC) is strongly recommended <http://isites.harvard.edu/icb/icb.do?keyword=k69586andpageid=icb.page334798>
- Research on OPC in developing countries should prioritize oral health as part of general health and generate policy-shift toward integrated care.
- Despite immense needs and opportunities for basic science research, application of existing knowledge should take priority.

BASIC SCIENCE

Each cancer is a unique biological event in a unique host; an inherited predisposition and host response factors may be as important as direct etiological factors. In an era of personalized medicine, caution is required when generalizing from population-based molecular studies. An example of this is the demonstration that HPV-related SCC could be a distinct subset (Ang *et al*., 2010).

The literature on screening for individual markers has been reviewed (Pitiyage *et al*., 2009), and, in the wake of whole-genome analysis, a review of existing knowledge about which molecular markers might help predict malignant transformation within OPMD has recently been published (Lingen *et al*., 2011). The International Cancer Genome Consortium (ICGC), http://www.icgc.org/, is likely to deliver critical information, but caution is essential in interpreting pooled results. The extent to which any marker, or panel of markers, can be applied to an individual case will always be only a statistical probability. Work on oral cancer for the ICGC has been allocated to The Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Navi Mumbai, India, http://www.icgc.org/icgc/cgp/63/423/823.

Priorities for Research

- Creation of well-managed tissue, blood, and saliva banks from as many distinct population and risk groups as possible, using common protocols. Dental care and research institutions are a major source of such material. The IADR is uniquely placed to lead the organization of such networks, in concert with existing structures, notably the ICGC.
- This is “big science” and expensive. It is essential to work with major research bodies, such as NIH, WHO, IARC, MRC (UK), Wellcome, Sanger Institute, and other funders such as the Gates Foundation.

CONCLUSION

Few public policies around the world have addressed oral cancer incidence and poor outcomes (Torres-Pereira, 2010). Prioritizing our recommendations to focus on inequalities is challenging. IADR, FDI, dental research organizations, and funders worldwide must truly engage with other health professions and their national or international bodies, with governments, NGOs, and the public to plan joint work. Much pragmatism will be required. Things will be achieved where enthusiasms reign. Actions will, to a degree, be idiosyncratic. Funding constraints and lack of political will are always with us.

ACKNOWLEDGMENTS

The author(s) received no financial support and declared no potential conflicts of interests with respect to the authorship and/or publication of this article.[AQ: 3]

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