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Perspective on oral cancer screening: time for implementation research and beyond

Brief title: Oral cancer screening perspective

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In the last 30 years, cancer management globally has seen an upswing in the importance of prevention and early detection of cancer and precursor lesions. Cancer early detection programmes, such as screening, have become an integral part of health care systems in high income countries.[1-3]

Screening aims to detect cancer in asymptomatic populations. This allows to shift detection from advanced to early stages, and potentially decrease cancer-related mortality. For some cancers, such as cervical and colorectal cancer, screening can also detect precursor lesions, which, when treated appropriately, leads to decreased cancer incidence. On the other hand, screening may be accompanied by related harms, such as overdiagnosis leading to over treatment, and false positive results. These harms imply unnecessary diagnostic or treatment procedures, consequently resulting in additional physical, psychological and financial harms for the patients, and in wastage of healthcare capacity and resources. Thus, the decision to implement screening must be based on a balanced consideration of the benefits and harms of a screening programme and numerous other factors, such as cost-effectiveness, feasibility, affordability, and health system readiness.[4-6] For the three widely recommended cancer screening programmes – for cancers of the cervix uteri, breast, and colorectum – substantial clinical and economic evidence have supported the implementation of different screening strategies defined by the screening method, screening interval, and population characteristics such as age and sex, as well as specific regimens for defined high-risk populations.[4,7,8] This aggregate of evidence, unfortunately, is lacking for oral cancer screening.

Oral cancer is an umbrella term that encompasses malignant neoplasia that arises on the mucosal lip and the many sub-sites in the oral cavity. The risk for oral cancer is associated primarily with the use of tobacco in all forms and alcohol consumption. [9,10] The International Agency for Research on Cancer Global Cancer Observatory (IARC GLOBOCAN) estimated 377,713 new cases and 177,757 deaths from oral cancers worldwide in 2020.[11] The estimated number of incident cases of oral cancers ranked 16th among all cancers (for both sexes); combined with cases of oropharyngeal cancers the rank increased to the 13th most common cancer worldwide. Notably, it ranks among the top three most incident cancers in Bangladesh, India, Sri Lanka, Pakistan and Papua New Guinea.

Clinical oral examination is the current standard method for oral cancer screening and is usually performed by a dentist, a physician, or primary healthcare workers such as nurses or community heatlh workers after appropriate training, thus is an affordable and feasible method.[12] Two systematic reviews have evaluated the effectiveness of oral cancer screening programmes. [13,14] These reviews were based on a single cluster-randomised trial in Kerala, India and recommended further randomised controlled trials to assess the efficacy and cost-effectiveness of clinical oral examination as part of a population based screening programme. The just-mentioned cluster-randomised trial in India had 15 years of follow-up and reported a 81% mortality reduction in high-risk populations of tobacco and/or alcohol users who adhered to four screening rounds.[15-17] However, this trial suffered from a limited compliance with referrals (around 50%) among those who screened positive;[16] This, on the one side exposes the complexity of adehrence to protocol in high-risk population, and on another side suggests that higher impact of screening on advanced cancer diagnosis and mortality may be acieved with higher compliance rate. In addition to the trial, the few observational studies that have reported on the effectiveness of national oral cancer screening programmes are subject to design limitations and biases, such as in the definitions of cases and controls and risk of their miss-classification, information bias, and poor compliance with referrals. Nevertheless, the available studies report quite similar impact of oral cancer

screening by clinical oral examination in terms of reductions in advanced oral cancer (21-22%) and oral cancer mortality (24-26%) among high-risk populations[15,16,18].

Besides the limited clinical evidence, the economic rationale behind implementation of oral cancer screening is weak and would only apply to the settings were data are available (i.e. India)[19], given the questionable applicability of these results to other jurisdictions.[15,18] Nevertheless, the relatively low costs of such screening programmes suggest a potential cost-effectiveness among high-risk populations in low-and middle-income settings, which needs to be confirmed empirically.[19]

Considering the high prevalence of oral diseases, the World Health Organization (WHO), grounded on the spirit of the United Nations Development Programme's report "Think globally act locally", established the first Global Oral Health Goals in 1981. The Global Goals for Oral Health 2020, developed as a joint initiative between FDI/IADR and WHO, were updated in 2003, to stimulate awareness about the importance of oral health across the nations and the governments. Among the updated objectives of the WHO were a reduction in morbidity and mortality from oral diseases, as well as the promotion of cost-effective interventions to prevent and manage oral diseases.[20] Despite these ambitious goals, the WHO commitment, and the evidence of reduced oral cancer mortality, screening of high-risk populations for oral cancer is implemented on either national or regional levels only in a few countries with comparatively high incidence rates for oral cancer, such as in India, Cuba and Taiwan.[15,18] The recent WHA74.5 resolution on oral health adopted in 2021 is a strong political commitment by Member States that gives a unique mandate to WHO to reposition oral diseases, including oral cancer, as part of the global health agenda towards 2030.

The lack of implementation of or pilot projects for oral cancer screening may be partially related to the scarcity of experimental studies and so the unsupportive conclusions from the Cochrane systematic reviews[13,14], shading the seemly optimism around a potentially-effective, easy to implement, and low-cost oral cancer screening. At this moment, the described paradox might not be addressed by more clinical trials, which are more difficult to initiate for oral cancer than other cancer screenings because of the geographical prevalence of the disease in low-resource settings and the lack of interest and involvement from the industry.

It is time to move forward with the evidence we bear and tackle the ongoing and urgent need to reduce morbidity and mortality from oral cancer in populations with a high prevalence of disease through investments in pilot oral cancer screening programmes and well-designed implementation research assessing their performance. The priority actions will include initiation of the oral cancer screening programmes for high-risk populations as adds-on to the existing public programmes (eg. current and former smokers screened for lung cancer[21]) or as independent pilots in countries with high disease prevalence (Box 1). These pilots will be able to gather necessary data to inform framework-guided implementation and service outcomes,[6] necessary for the nation-wide decisions on oral cancer screening.

Thus, to support WHO new goals on global oral health further, the authorities are urged to fund, and the implementers to organise and evaluate properly, oral cancer screening programmes to maximise health benefits of high-risk populations globally.

Box 1. The priority steps for development and implementation of oral cancer screening agenda

1. **Pilot screening programmes:**
   1a Adds-on to tobacco cessation and lung cancer screening programmes (when context is appropriate)
   1b New screening programmes for high-risk population and in areas with high disease prevalence
2. **Data collection from the pilots:**
   2a Disease detection and health impact of related interventions
   2b Screening uptake, compliance and its determinants
   2c Resource use
   2d Costs
3. **Future research:**
   3a Long-term outcomes, harms (overdiagnosis), and cost-effectiveness
   3b Penetration
   3c Programme sustainability.
4. **National implementation**

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