Oral cancer screening: 5 minutes to save a life

In today's *Lancet*, Rengaswamy Sankaranarayanan and colleagues report the first solid evidence that periodic examination of the oral cavity can reduce mortality from oral cancer in high-risk individuals. These results come from the Kerala screening trial, a cluster randomised trial, designed to have 80% power to detect a 35% reduction in oral cancer mortality within 12 years of enrolment between the intervention and control group, through rounds of screening every 3 years. The investigators report that, 9 years after the start of screening, there was a significant 32% reduction in mortality in high-risk individuals in the intervention group (42% when only male tobacco/alcohol users are considered). Overall, these data suggest that oral visual screening in high-risk patients could prevent about 40 000 deaths from oral cancer worldwide.

The reported data could be read in two ways. The first is the methodological evaluation of oral cancer screening itself. From this point of view, are the outcomes reported by Sankaranarayanan and colleagues adequately supported by the study design or do limitations exist? For example, the restricted-block randomisation can be potentially imbalanced when the number of clusters is small. Also, the recruitment of non-medical health workers raises concerns about the sensitivity and specificity to detect lesions and patients' compliance with referral. A screening interval of 3 years is long and the percentage of patients who did not get biopsy was high. Finally, clinical and histopathological diagnostic criteria were not clearly reported and variations in definitions and management of oral lesions can influence screening outcomes. On the other hand, the data suggest perhaps the right perspective in the fight against oral cancer—supporting prevention through screening as a potential major target of every health organisation worldwide. Oral cancer is a significant public-health threat, accounting for 270 000 new cases annually[1] and with one of the lowest survival rates (fewer than 50% of patients surviving more than 5 years). Furthermore, in the past few decades despite advances in the detection and treatment of many other malignancies, this rate has remained disappointingly low and relatively constant.

Rather than prevalence, the most peculiar characteristic of oral cancer is the apparently unexplainable imbalance between its global burden and the potential theoretical ease in decreasing morbidity and mortality with early detection. Oral cancer is almost always preceded by visible changes in the oral mucosa (figure, A and B), which allows clinicians to detect and treat effectively early intraepithelial stages of oral carcinogenesis.[2] Nevertheless, most oral cancers are currently detected at a late stage, when treatment is complex, costly, and has poor outcomes (figure, C and D). Paradoxically, the percentage of oral cancers diagnosed in the early stages is similar to that of colon cancers (36%).[3] Lack of awareness in the public of the signs, symptoms, and risk factors for oral cancer,[4] as well as a disappointing absence of prevention and early detection by health-care providers,[5] are both believed to be responsible for the diagnostic delay. It is strange to think that, at present, pelvic examination and Pap smears appear more acceptable than looking in the mouth,[6] for both patients and physicians. Current research mainly focuses on therapies for advanced oral cancers. As a result we have been spending hundreds of millions of dollars in treating patients, two-thirds of whom will die within 3–5 years, consuming educational

See **Articles** page 1927

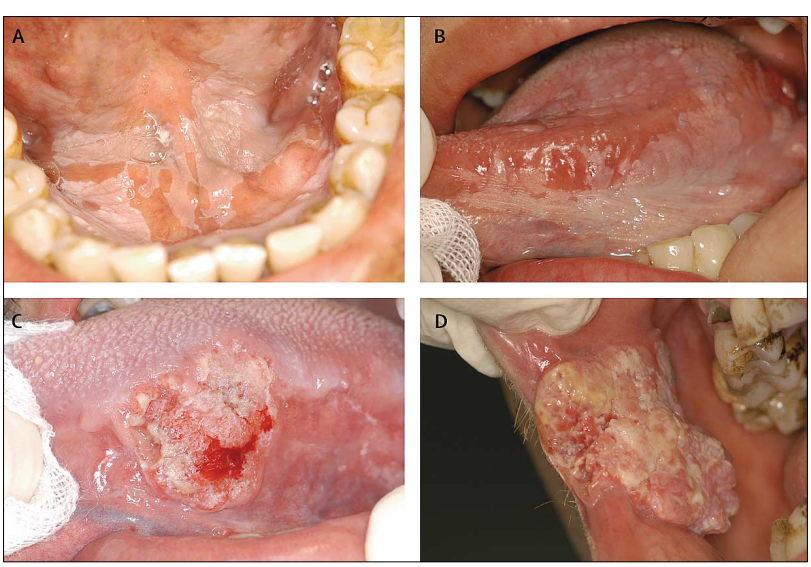


Figure: **Oral precancer and cancer**
5-min clinical examination of oral mucosa with only lighting, gauze, and gloves can easily detect potentially malignant lesions (A=leukoplakia of floor of mouth; B=leukoplakia of tongue). Identification should allow clinicians to detect early intraepithelial stages of oral carcinogenesis, such as mild, moderate, and severe dysplasia, and carcinoma in situ, which generally precede development of invasive oral squamous-cell cancer and, if appropriately managed, are often characterised by good prognosis. Nevertheless, most oral cancers are currently diagnosed at late stage (C=advanced cancer of tongue; D=advanced cancer of buccal mucosa), when local and lymphatic spread are already present, leading to a dramatically worse prognosis and increased treatment costs.

and scientific resources on procedures burdened by high costs and poor results, or on expensive molecular studies that are not easy to reproduce or can be applied to a small percentage of patients only.[7] It is now time for a new deal.

A first step has already been taken by WHO, which has recently issued a commitment to action against the neglected burden of oral cancer, mainly by strengthening prevention.[8] Nevertheless, so far, there has been no evidence to support the use of visual examination as a method of screening for oral cancer.[9] Sankaranarayanan and colleagues' data should lead health organisations to change, at least in part, their policy, transferring resources from conventional fields to new methods of preventive intervention with greater effectiveness and lower cost. We have to remember that screening for oral cancer is a simple non-invasive procedure, which needs only a 5-min visual inspection of the oral mucosa with lighting, gauze, and gloves, whereas the detection of most solid malignancies in their early asymptomatic stages almost always requires special, costly, and often invasive techniques. Visual screening for oral cancer is easy, effective, cheap, and saves lives.

*Michele D Mignogna, Stefano Fedele
Division of Oral Medicine, Department of Odontostomatological and Maxillofacial Sciences, University of Naples "Federico II", 80129, Naples, Italy
mdmig@tin.it

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Immune-mediated attack in relapsed Hodgkin's lymphoma

See Articles page 1934

About 80% of patients with Hodgkin's lymphoma are likely to be cured by first-line chemotherapy. Of those who relapse and undergo a salvage treatment, usually with autologous transplantation, 40–50% will have recurrence. These patients are potential candidates for an allogeneic stem-cell transplantation, but since they are a minority of Hodgkin's lymphoma patients, very few prospective trials have assessed the real benefit of the procedure. The Seattle group[1] reported a long-term follow-up study in which relapsed or refractory Hodgkin patients received allogeneic or autologous bone marrow transplantation. They compared allogeneic identical sibling versus autologous transplants and showed a non-significant difference in event-free survival rates (26% *vs* 14% 5-year actuarial estimate, p=0·6) and non-relapse mortality rates (53% *vs* 43%, p=0·2), but a significantly lower relapse rate among the allogeneic transplants (45% *vs* 76%, p=0·05). Also the Johns Hopkins group[2] reported a long-term follow-up study in which only chemosensitive relapse patients developing graft-versus-host disease had a trend for a better outcome. Actuarial relapse probability among the patients with graft-versus-host disease was 14% (range 0–40%) compared with 55% (13–96%) among the patients without graft-versus-host disease (p=0·24).[1,2] Taking into account that in both studies the allografted patients had more adverse prognostic features, the results are interesting and support the notion that a graft-versus-tumour effect is probably present. Such an effect was suggested by Porter et al[3] who treated relapsed/refractory patients with infusions of donor lymphocytes not preceded by a transplant: one patient who developed acute graft-versus-host disease had a response. Our impression is that a clinical response, after lymphocyte infusion only, can be considered a proof of principle that an immune-mediated graft-versus-tumour effect does exist in Hodgkin's lymphoma (figure). Nevertheless, whether this effect can alter the outcome for relapsed or refractory patients is unknown. Retrospective studies from European and international