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Reviews

European School of Oncology Advisory Report to the European Commission for the Europe Against Cancer Programme: Oral Carcinogenesis in Europe

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A European School of Oncology Advisory Group has reviewed current knowledge on the epidemiology, treatment and prevention of cancer of the oral cavity. While the major factors in the aetiology of such cancers are thought to be well understood, i.e. tobacco and alcohol consumption, current increases in the occurrence of the disease, especially in young adults throughout Europe, are cause for concern. The reasons for such increases are not clearly evident and the Advisory Group has suggested further work which is required to be carried out to understand the aetiology. In treatment of the disease there have been no major improvements in survival for patients in recent decades and the importance of examining new radiotherapy modalities and defining the role of chemotherapy is emphasized. Primary prevention of oral cancer could be achieved by stopping smoking tobacco, limiting alcohol consumption to a minimum (2–3 drinks per day) and increasing intake of fruits and vegetables. To supplement these actions, while neither population screening programmes nor screening trials could be recommended by the Advisory Group, initial chemoprevention trials have produced some promising results and this represents an interesting area which is the focus of much current research.

Keywords: oral neoplasms, epidemiology, treatment, chemoprevention, screening

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INTRODUCTION

THIS IS the report of the European School of Oncology Advisory Group on Oral Carcinogenesis which met during April 1994 in Milan, Italy. The Advisory Group reviewed current knowledge and assessed future prospects in the following areas: epidemiology, treatment, chemoprevention and screening. Thereafter recommendations of aspects in oral carcinogenesis which the Advisory Group felt should be a particular focus of attention are presented. This report represents the final version which was approved by the EC Cancer Experts at their meeting in Bonn, Germany, 28–29 November 1994.

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ORAL CANCER EPIDEMIOLOGY

Descriptive epidemiology

Between 1978 and 1982 an estimated 32 300 new cases of oral cavity cancer (ICD-9 140-9) [1] were diagnosed every year in the European Community (EC) and 18 000 persons died from the disease [2]. The vast majority of incident cases occurred in males (27 300) in whom it represented 4.2% of all cancers, while among females the 5000 cases represented 0.9% of all cancers diagnosed. Oral cavity cancer is a particular problem among males in France; the estimated incidence rate of 33.9 per 100 000 is exceeded only by cancers of the lung and prostate and, in some areas of the country, cancer of the oral cavity is the most common form of cancer death [2, 3]. In addition high incidence rates are also reported from the central European countries of Slovenia, Slovakia, Switzerland and Hungary [4].

The following report relates mainly to cancers of the tongue

(ICD-9), mouth (ICD-9 143-5), hypopharynx and oropharynx (ICD-9 146, 148). Lip cancer, which has a distinct descriptive and analytical epidemiology, will be considered separately. Cancers of the salivary glands and nasopharynx have not been included. First because the epidemiology of these tumours are quite different and second because in European populations both types of tumour are comparatively rare.

Lip cancer. The highest rates of lip cancer of around 10 per 100 000 (males) are recorded in parts of Australia, Spain and Canada [4]. However, the general world-wide pattern is of decreasing rates among males such that it is now an uncommon disease in most areas of the world [5]. In females, incidence rates have historically been low and this situation remains unchanged with few registries reporting rates over 1.0 per 100 000 [4].

With low frequency of occurrence and high survival rates, mortality from lip cancer is very low. The highest rates in males of around 4 per million person years occur in central and eastern Europe, with most other countries recording rates of below 2 per million person years. Among females, mortality rates rarely exceed 0.5 per million person years [6].

Cancers of the tongue, mouth, hypopharynx and oropharynx. Cancers at these sites have very similar descriptive epidemiological features and will be considered together. The most common areas of occurrence in males are France and India with rates of between 20 and 50 per 100 000, considerably above those reported elsewhere. High rates are also reported from countries in central Europe: Switzerland, Slovakia, Slovenia and Hungary. In contrast consistently low rates in males are reported from China and Japan and countries of northern Europe [4].

In females the highest rates are between 5 and 10 per 100 000 and are found in India, countries of South-east Asia and the United States of America. The high rates of intra-oral and pharyngeal cancers in men in France do not occur in women and similarly the high male rates in central Europe contrast with the extremely low rates of these diseases among women [4].

During the 1950s, 1960s and 1970s descriptive epidemiological reports noted continuing decreases in mortality from and/or incidence of intra-oral and pharyngeal cancers. Such decreases were recorded in the United States, Australia and countries of western, central and eastern Europe [7–11]. The pattern of continuing decreases thereafter began to change. This was first indicated by the observation of increasing incidence of, and mortality from, tongue cancer in the United States and increasing incidence of intra-oral and pharyngeal cancer in both sexes in Denmark [12–14]. The reasons for such increases, however, were attributed to different agents. In the United States it was believed to be consistent with increasing use of smokeless tobacco especially amongst young males [15] while in Denmark it was postulated to be due to alcohol consumption [14]. Subsequently, examination of further trends in incidence of intra-oral and pharyngeal cancers showed increases in rates among males in other European countries and in Australia [16–20]. There was no consistent increase, however, recorded amongst females.

A notable observation, however, about these increasing rates was the similarity in the way in which they were changing. In Scotland, Denmark and Slovakia changes in rates primarily occurred by birth cohort with rates increasing for those born after 1915. Rates have continued to increase with later-born cohorts.

These observations in incidence data for males have been confirmed with analysis of mortality data which are available to a greater extent world-wide. These show consistent results: decreasing risks of dying from oral cancer for those born after 1870 whereas for those born from around 1915 onwards risks have been increasing once more. The largest changes in risk have occurred in central and eastern Europe where risks have increased between 3- and 10-fold for those born in 1940 compared to 25 years previously. Only four of the 24 countries examined did not conform to this changing pattern of rates: United States, Japan, Sweden and Finland [21]. In contrast, no such consistent pattern of increasing mortality rates is noted for females [22].

Although some of the increasing rates may be due to artefactual causes, such as changes in registration practices, it seems unlikely that this is a major factor in the currently increasing rates since:

similar trends are observed for both incidence and mortality;

the increase in incidence and mortality in most countries has occurred primarily in men;

similar trends have occurred in many countries, particularly throughout Europe;

similar trends are observed at adjacent sites within the oral cavity which share a similar aetiology;

cancers of the salivary glands and nasopharynx with a diverse aetiology to tumours of the remainder of the oral cavity and pharynx, do not exhibit similar increases in males;

analysis of long-time series of incidence and mortality rates have shown rates to be changing by year of birth.

Although, therefore, these changing incidence and mortality rates are considered to be real, the likely cause is unknown. In particular it is unknown whether it is the same factor which is responsible for increases in different countries or whether the increases are due to well established risk factors such as tobacco smoking and/or alcohol drinking or to some other factor(s).

Analytical epidemiology

The major causes of oral cancer in most populations are tobacco smoking [23] and alcohol consumption [24]. Other determinants have also been identified which may influence risk of these cancers on their own or modify the effects of tobacco and alcohol. A brief review of current issues in risk factors for oral cancer follows.

Tobacco. Together with the drinking of alcoholic beverages, use of tobacco (primarily via cigarettes) accounts for about 75% of all oral cancers in the United States and many other countries [25–27]. Risk appears to drop rapidly following cessation of cigarette smoking [25, 28, 29], but further work is necessary to clarify the carcinogenic stages affected by tobacco. Risk variation by type of cigarette has been reported, with higher risks for high-tar brands [30] and no extra risk for mentholated cigarettes commonly smoked by Afro-Americans in the United States [31] or dark tobaccos smoked in some European and Latin American countries [32], but data on such differences are sparse.

Smokeless tobacco, used in parts of the United States, Europe and south Asia, can induce oral cancers [33]. Whether the effects of oral snuff, still popular among American youth, differ from effects of chewing tobacco is not clear, and whether

ingredients besides tobacco in pan and other Asian chews influence risk requires confirmation.

Alcohol. Heavy drinking of alcoholic beverages clearly can cause oral cancer, with tobacco and alcohol typically combining in a multiplicative fashion to enhance risk. Most of the excess is associated with consuming more than two drinks of alcohol/day, with the shape of the dose–response curve at lower doses not precise. Multiple types of alcoholic beverages have been associated with oral cancer, indicating the primary role of ethanol, although other ingredients may also be involved. The mechanisms by which alcoholic beverages induce oral cancer are not well understood: a late-stage effect has been postulated, but clear information on risks according to timing of exposure, and on changes in risk following cessation of drinking is unavailable and requires further study.

Diet and nutrition. Epidemiologic studies have consistently found that oral cancer patients typically have had lower intakes of fresh fruit and vegetables when compared with healthy controls [34]. The data are sufficiently strong that a fruit and vegetable rich diet can be recommended, but the responsible ingredients are not known and neither is the daily amount needed to confer protection. The antioxidants vitamin C, beta-carotene and vitamin E may be protective factors. Both beta-carotene and vitamin E have been shown in clinical trials to reverse precancerous oral lesions (mainly leukoplakia) [35–37], and vitamin E has blocked oral cancers in experimental animals [38]. Use of vitamin E supplements in the United States has also been associated with reduced risk [39, 40]. High doses of synthetic retinoids have inhibited the onset of second primary cancers in oral cancer patients [41], although dietary retinol may not have similar effects. Further research on specific nutrients is needed to help clarify the prevention potential of vitamins and minerals and delineate whether other components of fruits and vegetables may be protective.

Oral hygiene. Despite being long postulated as a risk factor for oral cancer, the association with poor oral hygiene, independent of tobacco and alcohol consumption, is not clear. Poor dentition appears to be linked to increased risk [28, 42, 43]. Mouthwashes high in alcohol intake have also been implicated [44], but confirmation is needed in other studies.

Occupation. Occupational factors probably play at most a small role in oral cancer aetiology. Increased rates of oral cancer have been reported among workers exposed to asbestos, mineral fibres, and several other substances, indicating a need for continued workplace observations.

Genetic predisposition. Oral cancer tends not to cluster strongly in families, with recent data from a large United States survey showing only slight increases in risk among persons with family members with oral cancer [45]. Markers of individual susceptibility, however, such as polymorphisms in p450 genes that regulate metabolism of tobacco and other carcinogens, are continuing to be sought and may help explain variation in risk by racial and other host characteristics.

Viruses. Viruses have been implicated in cancer development in other squamous epithelia, and it is conceivable that viruses might contribute aetiologically in at least some cases of oral carcinoma [46]. Indeed a recent epidemiological study concluded that HPV-6 was associated with oral cancer. However, it should be noted that the study had a low response rate and that biological samples were taken from cases after removal of the tumour [47]. Since HPV-DNA was first detected in oral squamous cell carcinomas in Germany in 1985 [48, 49] this observation has been confirmed by several groups who find predominantly the "genital" types of viruses, namely HPV-6, 11 and 16. However, HPV have also been detected in apparently normal mucosa [50, 51], so it is necessary to remain cautious about its role in aetiology. Recent studies have given an insight of how complex and subtle the role of HPV might be in cancer development. It has been hypothesized that a defect in intracellular surveillance mechanisms might be important in HPV-associated oncogenesis [52]. One interpretation of this hypothesis is that specific cellular defence mechanisms acting against cancer development (i.e. anti-oncogenes) might possibly be mutated by viruses. It has now been shown that the HPV 16 E6 and E7 gene products may be able to act in such a way, binding various human gene products, particularly the *p53* and retinoblastoma genes [53], and thereby possibly deregulating control of cell proliferation and differentiation.

Studies of the association of HSV with human oral carcinoma have shown changes in levels of HSV antibodies, but examination of human oral carcinoma tissues for HSV viral "footprints" has given somewhat equivocal results. Nevertheless, a failure to demonstrate HSV products, does not, of course, exclude a "hit and run" mechanism of oncogenesis, i.e. the virus might cause genetic damage but then not itself remain present [54]. HSV antigens have been shown in carcinomas in some [55] but not in all studies [56]. Demonstration, by *in situ* hybridisation, of RNA complementary to HSV-DNA in biopsies from oral carcinoma but not from autologous, normal oral mucosa, further suggested an association of HSV with oral carcinoma [57] and other workers have subsequently demonstrated HSV-1 DNA in oral carcinoma tissue [58]. Of course, the presence of HSV does not prove a causal association: the only real proof can come if it can be shown that immunisation against the virus prevents tumour development.

Clearly there have been many potentially interesting observations on the possible role of viruses in the study of oral carcinogenesis, but further areas need to be researched before such viruses can be causally implicated in the aetiology of the disease.

ORAL CANCER TREATMENT

Oral malignancies can be treated using various modalities. As a general rule, early disease is treated by either surgery or radiotherapy (in particular by brachytherapy). The choice between these two modalities depends on the size and the location of the primary tumour, on the proximity to the mandible and the status of the teeth, on the age, wishes and compliance of the patient and, also, on the clinician's preferences and experience. Moderately advanced lesions are treated in accordance with consensus protocols. If tumours are at a distance from the mandibular arch they are treated similarly. In contrast, when the mandible is involved, there is a consensus for surgical resection with postoperative radiotherapy only in the case of close or positive margins or of nodal involvement. When resectable, locally advanced tumours are surgically treated with postoperative radiotherapy in all cases.

Palliative treatments for unresectable diseases consist of radiotherapy with or without chemotherapy. Except for T1 (T2) N0 lesions, the treatment of the neck is always associated with the management of the primary.

Cancer of the lip

Precancerous or superficial lesions are treated by vermillonectomy which allows a complete resection of these very early tumours and provides a good specimen for a complete pathology evaluation. T1 and T2 lesions are treated either by interstitial radionucleide implants or surgery. There are numerous efficient plastic surgery procedures that lead to acceptable cosmetic results after tumour resection. The control rate is excellent, ranging between 85 and 95%, whatever the type of treatment. When resectable, larger tumours are treated by wide surgery with flap reconstruction and postoperative radiotherapy. The local control ranges from 50 to 60% and is very low when there is a bone extension. Unresectable tumours are treated by external radiotherapy with palliative intent.

Cancer of the floor of mouth

Precancerous changes and superficial lesions can be treated by transoral carbon dioxide laser surgery (excision or evaporation) or classical electrosurgery (excision and/or coagulation).

T1 tumours at a distance from the mandible can also be transorally treated but each time the tumour is bordering, fixing or involving the mandibular arch or each time the presentation of the tumour is such that it could not be properly resected (risk of positive margins or of fragmentation of the tumour, for example) comprehensive surgery is required. That is also the case for T2-4 resectable tumours. This surgery consists of a mandibular resection in continuity with the tumour and, in almost all cases, with the neck dissection.

If the tumour is extending to less than 1 cm from the bone, a rim resection provides good surgical margins. This kind of marginal mandibulectomy is also indicated when the mandible is involved for less than half its height. In this type of mandibulectomy, there is no interruption of the mandibular continuity and, subsequently, no need for mandibular reconstruction. The mucosal defect is closed directly or thanks to a nasolabial flap, a platysmal myocutaneous flap, or rarely a pectoralis major myocutaneous flap. Sometimes with surgery, the dental prosthesis adaptation is quite difficult, in particular in edentulous patients or when a flap is covering the mandibular defect. Titanium osseo-integrated dental implants are of interest for fastening the prosthesis. When the mandible is deeply involved, then a segmental mandibulectomy is required. The mandibular discontinuity must be repaired with metallic sheets or, better still, with bony free transfers with microvascular anastomoses (in particular the fibula free transfer). When the tumour is involving the most posterior part of the floor of mouth or of the mandible, a hemimandibulectomy is required. In that case, the mandibular reconstruction is less easy.

T1 and T2 tumours remaining at a distance from the mandible are also suitable for iridium implants. Brachytherapy provides results as good as surgery in terms of local control when used alone. In contrast, combinations of external radiotherapy and brachytherapy are less efficient. Large tumours not suitable for surgery are treated by external radiotherapy after induction chemotherapy for very advanced tumours. Such induction chemotherapy has, at the moment, no place in the treatment of early or moderately advanced disease.

According to the staging, local control ranges between 90% for T1 to 40% for T4 lesions and the 5-year survival from 75 to 25%.

Cancer of the oral tongue

T1 and T2 lesions are treated by either brachytherapy or transoral surgery with similar control rates and with, overall, similar functional results. Larger tumours are more often cured by combined treatment than by radiotherapy alone, but sequelae are notable. In order to get an appropriate view of the surgical field, a transmandibular approach (mandibular swing) is often necessary. For tumours involving the floor of the mouth, a marginal mandibulectomy provides better access to the tumour and, for tumours involving the mandible, a hemimandibulectomy is often necessary. Very extensive tumours may require a total glossectomy with or without laryngectomy but such procedures must be carefully discussed due to the importance of sequelae and the very low control rate. The tongue volume can be reconstructed thanks to myocutaneous flaps or, in selected cases, thanks to free transfers. If interstitial irradiation is able to cure early stage mobile tongue cancers, in contrast external irradiation is most often palliative for advanced diseases.

According to the staging, local control ranges from 90% for T1 to 30% for T4 lesions and the 5-year survival from 70 to 15%.

Cancer of the lower gingiva (including the retromolar trigone)

Surgery is, by far, the most common treatment. Marginal or segmental mandibulectomies or hemimandibulectomies are indicated according to the degree of bony extension. The mucosal and mandibular reconstruction is similar to cancer of the floor of the mouth.

According to the staging, local control ranges from 70% for T1 to 25% for T4 lesions and the 5-year survival from 60 to 25%.

Cancer of the upper gingiva and hard palate

Surgery is, as for the lower gingiva, the main treatment and surgical resection is adapted to the tumour volume ranging from a partial maxillectomy to a total maxillectomy for advanced and posterior lesions. Postoperative radiotherapy is indicated for large tumours extending to the surrounding tissues. According to stage, the 5-year survival ranges from 60 to 30%.

Cancer of the buccal mucosa

This primary site is the most difficult oral cavity tumour to cure. According to the precise site and size of the tumour, the proximity of the mandible, maxilla or commissure, surgery or radiotherapy is indicated.

According to the staging, local control ranges between 70% for T1 to 5% for T4 tumours and the 5-year survival from 60 to 5%.

Management of the neck

When the primary tumour is treated by surgery or brachytherapy, except for T1 (T2) N0 lesions of the lower

gingiva and hard palate, the treatment of the neck is systematically associated. Most often, a total neck dissection is performed, bilaterally if the midline is reached. For early lesions of the anterior floor of the mouth, without palpable lymph nodes, some authors perform only a supraomohyoid neck dissection. In contrast, for tumours of the buccal mucosa, the neck dissection is often extended to the parotid area. According to the presence or absence of a palpable lymph node and the size of the largest lymph node, the dissection is radical or modified (functional). In the case of nodal involvement postoperative irradiation is given to the neck.

When the treatment of the primary tumour is by external radiotherapy with curative intent, the neck is also irradiated. In the case of a palpable lymph node over 3 cm in diameter, a neck dissection is performed prior to radiation or reserved for salvage after radiotherapy, on an individual basis. As a general rule, the presence of a palpable lymph node over 3 cm in diameter halves the prognosis and the presence in the specimen of a capsular rupture, multiple nodal involvement, or lower neck involvement has a deleterious impact on the outcome.

Pending questions and future prospects in treatment

At the moment, we have at our disposal numerous surgical procedures for tumour resection and reconstruction, in particular microsurgery and dental implants. It is unlikely that, in the near future, there will be revolutionary techniques.

New radiotherapy modalities (fractionation, acceleration, combination with chemotherapy) are under evaluation and preliminary results are promising. An improved correlation between imaging and computer dosimetry and the future development of conformation radiotherapy should improve the local control and the treatment tolerance.

To date there is no evidence that chemotherapy can improve the survival of patients with oral cavity cancer. The only advance could be the strategy of organ (mandible in this case) preservation with induction chemotherapy and "non mutilating" treatment in the case of complete response. For the future, we have to explore new drug regimens, the interest of other medical approaches such as biological response modifiers and, perhaps, gene therapy. In fact, the main problem seems to be to find adequate parameters (biological for instance) for allocation of patients to different treatment strategies.

CHEMOPREVENTION OF ORAL CANCER

As stated above, the incidence of oral cavity cancer is increasing throughout Europe, while long-term survival rates have not improved substantially over the last 30 years, despite intensive efforts in prevention and therapy [59]. Moreover, patients diagnosed early and treated successfully have an annual risk of developing metachronous carcinomas of about 4% [60].

The most obvious way to reduce the risk of oral cancer is to stop smoking tobacco and to reduce alcohol consumption to a minimum. These habits are, however, difficult to alter in populations. Increased consumption of fruits and vegetables could also serve to decrease the risk of oral cancer but such an intervention would be difficult to control and logistically impossible to assess in a randomised trial. Alternative new approaches are being tried to supplement these actions: chemoprevention is one of the more promising of these. Chemoprevention is defined as the use of natural or synthetic chemicals to reverse or suppress pre-malignant progression to invasive malignancy [61–64]. Theoretical support for chemopreventive intervention comes from the multistep and field carcinogenesis theories [65], while epidemiologic observations [66, 67] and experimental data [67, 68] provide empirical backup.

Multistep carcinogenesis is well-documented in pre-malignant lesions such as leukoplakia—a condition associated with a cancer rate of up to 20% over 20 years [69]. Recently leukoplakic lesions have been correlated with specific molecular genetic alterations: in particular reduced expression of retinoic acid receptors (RAR)-β, mutations in *p53* and *Ras*, and increased expression of TGF-α and *c-myc* [70].

The field carcinogenesis theory [71] supposes that a whole tissue region repeatedly exposed to carcinogenic insult—from substances like tobacco and alcohol—is at increased risk for developing multiple independent foci of malignant lesions. This hypothesis has recently received support by the finding that markers (molecular signs of carcinogenesis) are present in histologically abnormal mucosa, and in histologically, and also in clinically, normal epithelia within the upper aero digestive tract [72].

Many epidemiologic observations point to a correlation between diet and cancer. There have been numerous studies, for example, indicating a relationship between chronically low vitamin A or β-carotene plasma levels and the incidence of oral cancer [34, 73–75]. Other epidemiologic studies suggest that micronutrients such as selenium, vitamin E and vitamin C [66–68] may protect against cancer. These indications derive from active ongoing research on chemopreventive agents; however, it cannot be said that a protective action has been convincingly demonstrated, partly because of the wide distribution in foods of these substances, and because of the difficulty of obtaining objective dietary information [66].

Experimental data have shown retinoids to be effective inhibitors of experimental carcinogenesis at certain sites in animals, and to maintain normal growth and epithelial differentiation.

Chemopreventive agents

Retinoids (including vitamin A, β-carotene, 13-*cis*-retinoic acid, etretinate, and fenretinide) are among the most frequently studied drugs in chemoprevention [64, 76, 77]; however, many other agents have been shown to be effective in experimental studies including vitamin E, N-acetyl cysteine, selenium, and the substance oltipraz isolated from plants of the cabbage family. Approximately 300 agents are at present being tested *in vitro* or in animal experiments at the Division of Cancer Prevention and Control, of the National Cancer Institute, Bethesda [78]. Many of these substances, mainly retinoids, have been shown to control cellular differentiation and proliferation in epithelial tissues [79]. Their mechanism of action is not yet clear, but may be related to their antioxidant properties [78].

Chemoprevention studies

Currently, chemoprevention aims to control the early stages of carcinogenesis, and at the moment the only definitive endpoint of chemopreventive studies is cancer incidence. Clinical trials with potential chemopreventive agents therefore require large study populations and must continue for many years, so their costs are necessarily high [80]. And because chemoprevention involves basically healthy populations who

may or may not develop cancer, the methods of evaluating the results should be different from those in chemotherapy studies; furthermore, the agents administered must be well-tolerated and without side effects [81].

Several chemopreventive studies based on these criteria were performed in the 1980s and many others are ongoing. We can distinguish three types of chemopreventive studies, according to their goals:

Primary chemoprevention. Leukoplakias have been the first field of application of chemopreventive studies. These potentially malignant lesions are relatively frequent (although many countries cannot provide frequency estimates) and they are a good model for studies of chemoprevention because of their natural history characterised by possible development of recurrences, new localisations and carcinomas [82].

During the last 15 years, in several non-randomised studies, retinoids have sometimes proved to be efficacious in the treatment of precancerous lesions of the oral cavity. Up to now four randomised trials have been conducted on oral leukoplakias. Stich *et al.* [83] studied 130 patients using smokeless tobacco, divided into three groups: group I (35 patients) treated with β-carotene 180 mg/week; group II treated with β-carotene (180 mg/week) plus vitamin A (100 000 IU/week) and group III (35 patients) who received placebo. After 6 months of treatment a 15% remission in group I, 27% remission in group II and 3% remission in group III was observed. In a subsequent study Stich *et al.* [84] studied 65 tobacco/betal-nut chewers with well-developed oral leukoplakias. 33 patients received placebo and 21 vitamin A (200 000 IU/week) for 6 months. Complete remission was found in 57% of the patients and total suppression of the development of new leukoplakias in all chewers receiving vitamin A, compared to 3 and 21%, respectively, in the placebo group. In 1986, Hong published the results of a randomised study on 44 patients with leukoplakia. He found 67% remission in the 24 patients treated with high doses (1–2 mg/kg for 3 months) of 13-*cis*-retinoic acid (13cRA) versus 10% remission in 20 patients treated with placebo. However, toxicity was unacceptable for use in the general population and more than 50% of the responding patients relapsed within 3 months of intervention cession [85].

In order to assess less toxic doses and achieve better long-term results Hong *et al.* [70] designed a new randomised trial. 70 patients whose leukoplakia responded or remained stable following high-dose 13cRA induction therapy (1.5 mg/kg/day for 3 months) were randomly assigned to receive maintenance therapy with low dose 13cRA (0.5 mg/kg/day) or β-carotene (30 mg/day) for 9 months. Only 8% of the patients progressed in the low-dose 13cRA group, against 55% in the β-carotene group. Unfortunately, invasive or *in situ* carcinoma occurred in 7 patients from the β-carotene group and in 1 from the 13cRA group, and side effects were still significant in the 13cRA low-dose group [86].

We can conclude that retinoids appear to be effective in reversing oral leukoplakias, but they have side effects and there is no sure evidence of their effectiveness in reducing the risk of cancer occurrence. Moreover, schedules and intervention doses need further studies [70].

Adjuvant chemoprevention

Patients cured for a head and neck cancer are at high risk of developing a new primary tumour, mainly in the upper aerodigestive tract. This risk is estimated to be between 4 and 7% per year [60, 87, 88]. These considerations form the rationale for chemopreventive intervention after curative therapy of head and neck cancers. Four randomised studies were conducted in the 1980s and the results are available from three of them.

Chiesa *et al.* [82] randomised 165 patients operated on for oral leukoplakia, and with postoperative histology negative for cancer, to receive fenretinide (4-HPR) 200 mg/day for 52 weeks versus observation. The rationale of the study was that these patients were at high risk of developing local recurrences, new localisations, and cancer, after complete removal of their leukoplakia. The goal of the trial was to evaluate the effectiveness of 4-HPR in preventing these outcomes. A preliminary analysis, after 1 year of follow-up, showed that 22 relapses or new leukoplakias occurred in the control group against 11 in the 4-HPR group during the intervention period. This difference is significant, particularly for the occurrence of new localisations. Moreover, 4-HPR is less toxic than other retinoids [82]. Hong *et al.* [41] studied 103 patients who were disease-free after primary therapy for squamous cell carcinoma of the larynx, pharynx or oral cavity. They were randomly assigned to receive 13cRA (50–100 mg/m^2) or placebo, to be taken daily for 12 months. Significantly few second primaries were found in the 13cRA group, whereas there were no differences between the two groups as far as loco-regional recurrences or distant metastases were concerned. In 1993 a multicentric double-blind randomised trial was performed in France to evaluate the efficacy of etretinate in preventing second primary tumours in squamous cell carcinoma of the oral cavity and oropharynx. In this study 316 patients cured for a T1–T2 N0–N1 < 3 cm M0 oral or oropharyngeal cancer were randomised to receive either etretinate (50 mg/day for the first month and 25 mg/day for the following 23 months) or placebo. The 5-year survival and disease-free survival rates are similar in the two groups and there are no differences regarding local and regional relapses, distant metastases and second primaries [89].

Since 1988 the European Organization for Research and Treatment of Cancer (EORTC) has been conducting a multicentric chemopreventive study (Euroscan) in curatively treated patients with oral, laryngeal or lung cancers using N-acetyl-cysteine (NAC) and retinyl palmitate. NAC is believed to act in the early stages of carcinogenesis, before and possibly shortly after the occurrence of DNA damage. Vitamin A acts later, in the promotion and progression phases. Thus, the combination theoretically covers almost the entire carcinogenic process, with no expected interactive side effects [90]. The patients are randomised to receive NAC, retinyl palmitate, both of these, or placebo. The study is still ongoing and preliminary data show good compliance in treated patients and a low frequency of side effects [91].

In conclusion, these data, although limited, seem to show an effectiveness of some retinoids in preventing the development of new primaries, but do not seem to be able to halt the progression of treated disease. Moreover, further observation is needed to show how long the protective effect lasts.

Chemoprevention in high risk populations

Many epidemiologic studies point to a correlation between intake of certain vegetables and low risk of cancer. Also certain micronutrients have an inhibitory effect on cancer. In the last 6

months three randomised chemopreventive trials on large high risk populations have been published. Blot *et al.* [92] conducted his study on the people of Linxian in China—an area with one of the highest rates of oesophageal/gastric cardia cancer in the world, and also a persistently low intake of several micronutrients. The study began in 1985. 29584 adults were randomised to receive one of four nutrient combinations: (a) retinol and zinc; (b) riboflavin and niacin; (c) vitamin C and molybdenum; (d) β-carotene, vitamin E and selenium. Significantly lower total mortality, mainly from gastric cancer, was found in (d); the reduced risk began to be evident about 1–2 years after the start of supplementation. No significant effects on mortality rates have been found in the other groups [92].

Li *et al.* [93] conducted a 6-year prospective study in Linxian among persons with oesophageal dysplasia, randomising 3318 individuals with cytologic evidence of oesophageal dysplasia to receive a daily supplement containing 14 vitamins and 12 minerals, or a placebo. Persons receiving the supplement had an 8% reduction in death from gastric and oesophageal cancer compared with the control group; although this finding was not statistically significant.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Group recently published the results of a chemopreventive trial on 29 153 male smokers in Finland. The study was randomised, double-blind and placebo-controlled. The Finnish smokers were assigned to one of four regimens: (1) alpha-tocopherol (50 mg/day); (2) beta-carotene (20 mg/day); (3) both alpha-tocopherol and beta-carotene; (4) placebo. The authors found a *higher* incidence of lung cancer and ischaemic heart disease among the men who received beta-carotene. No reduction of lung cancer was observed among those who received alpha-tocopherol supplementation. No evidence of interaction between alpha-tocopherol and beta-carotene was found [94].

The conflicting results of these studies are intriguing. It may be argued that epidemiologic behaviour is likely to differ between Chinese and Finnish populations, for a variety of reasons. Firstly, normalisation of vitamin and micronutrient intake in the Chinese studies could be protective whereas the supplementation of the Finnish study could be harmful (or due to chance as the authors suggest in the discussion of their paper). In any case these data require further evaluation.

Intermediate endpoints in chemoprevention studies

Trials with cancer incidence as the endpoint are of long duration, and require large study populations [66, 67, 80]. This implies that chemoprevention trials require many more patients, longer follow-up and much greater costs than standard phase III chemotherapy trials. It is therefore felt that the use of intermediate endpoints would make prevention trials more feasible. This new field of research involves biomarkers as intermediate endpoints of carcinogenesis and it is hoped that this will lead to the development of cost-effective trials. Biomarkers include clinical markers, histological and cytological markers and chemoprevention trials require markers that reveal early carcinogenic changes and inform about the risk of malignant transformation. An ideal biomarker should meet the following requirements: (1) predict the response to chemoprevention; (2) monitor chemopreventive treatment; (3) be valuable in the selection of new chemopreventive agents; and (4) indicate the level of risk of malignant transformation. An example of the latter is given in the following. The value of a panel of monoclonal antibodies to identify biomarkers in oral mucosa associated with cancer risk has recently been investigated [95]. As a model, the expression of antigens was assessed in cytological preparations obtained from macroscopically normal oral mucosa of patients with tongue carcinoma and controls. The panel consisted of, among others, antibodies against cytokeratin 8, 10, 13 and 19. Oral mucosa of cancer patients had a more than three times increased expression of cytokeratin 19 as compared with controls (36.0 versus 11.3%, $P<0.01$), which makes it an interesting candidate as an intermediate endpoint [91].

The identification of suitable biomarkers would allow more chemoprevention trials to be carried out, in less time, using fewer patients. With respect to chemoprevention trials in leukoplakia, an efficient use of patients eligible for such intervention is particularly warranted since these patients are relatively rare as reflected by the small series of patients in chemoprevention trials and studies on oral leukoplakia.

In summary, the results obtained so far in chemoprevention are not completely satisfactory. The area still seems promising, but we do not yet have any gold standard chemopreventive agents. Clearly new chemopreventive agents, and combinations of them, should be tried. And many questions remain to be answered. For example, are chemopreventive agents really effective on normal mucosa in high risk patients? Could a panel of biomarkers be predictive? One way forward, as suggested by Schantz *et al.* [96], would be to design shorter studies on smaller populations using surrogate endpoints, and only chemopreventive agents effective in modulating biomarkers should be further studied in clinical trials with cancer incidence as an endpoint.

SCREENING FOR ORAL CANCER

Trends in life expectancy, coupled with the aging of the post World War II "baby-boom", will lead to an increase in coming decades in the absolute numbers of oral cancer cases diagnosed and deaths from the disease. This would occur even if current rates of oral cancer occurrence remained constant. The situation is, however, worsened by the presence of a temporal trend in risk in many countries together with an absence of significant improvements in treatment and with prospects of primary prevention poor. Therefore, a major effort is required to reduce the impact of these increases and reduction of mortality by screening has been proposed as one possible way to accomplish this.

In this context, screening involves the examination of asymptomatic men and women in order to classify them as likely or unlikely to have oral cancer. Men and women who are determined as likely to have the disease are investigated further to arrive at a final diagnosis: those found to have oral cancer are treated.

"Screening" in connection with early diagnosis and treatment should be clearly distinguished from other uses of the term in epidemiology and clinical practice. In particular, the term "screening" is commonly used to describe a series of tests carried out on a symptomatic patient for whom a diagnosis is not yet established. However, this type of screening is part of the practice of clinical medicine rather than public health or preventive medicine. It is also important to distinguish between diagnostic tests and screening tests. For example, while prostate specific antigen (PSA) determination may be a screening test for prostate cancer, a biopsy of the prostate is a diagnostic test. It is always important to distinguish between

screening and case-finding. Screening is aimed at the general population and not merely those who have sought some medical attention.

Owing to its easy accessibility and the knowledge that there are identified premalignant lesions, the mouth is an ideal target for screening programmes. In spite of this, widespread implementation of screening programmes for oral cancers cannot be recommended at the present time as public health policy. There are not adequate results available from randomised trials assessing screening for oral cancers. Randomised trials are the only methods of evaluation available which avoid bias. They are, by definition, large, complex and expensive. However, it is essential to have some indication of effectiveness and efficacy before embarking on such programmes. In particular there are a number of criteria which are considered necessary to be fulfilled. These criteria ("Wilson and Junger" Criteria) will be discussed individually.

I. *Is oral cancer an important public health problem?*

Oral cancer is an important public health problem, especially in men, and one which seems set to increase. It is particularly important on the Indian sub-continent, Republics of the former Soviet Union and parts of South-east Asia. It is and will continue to be an increasing problem in many countries of Europe.

This criterion appears to be fulfilled.

II. *Is there an effective treatment for localised disease?*

Identification of a lesion suspected as being premalignant can lead to successful therapy. Treatment of a small lesion (less than 2 cm) has a significant survival advantage over larger lesions (2–4 cm).

This criterion appears to be fulfilled.

III. *Are facilities for further diagnosis and treatment available?*

There would be pressure put on available facilities by the increased number of men and women, both true cases and false positives, needing further work, resulting from the implementation of a population-wide screening programme. Nevertheless, in the context of a randomised screening trial based within one or two geographical regions of a country, the resources necessary to cope with the resultant increased workload could be available.

This criterion appears to be fulfilled.

IV. *Is there an identifiable latent or early symptomatic stage for oral cancer?*

In a study in Sri Lanka, a visual examination of the mouth was performed with a positive test being defined by the finding of a white patch, red patch or ulcer. Some of these would be pre-malignant lesions. However, how many would be false positives? Sensitivity (the proportion of those who truly have the disease that are correctly classified as having it by the screening test) was found to be around 90%. A more pertinent question would be to know how many would have led to the development of malignant disease.

There remain several questions on the natural history of oral cancer which are required to be answered including: what percentage of oral cancers arise from an identified pre-malignant lesion, what is the malignant potential of various types of lesion, and does a premalignant lesion indicate a lesion-at-risk or a mouth-at-risk?

This criterion appears only to be partially fulfilled, if at all.

V. *Is the technique to be used for screening effective?*

In the case of oral cancer, the most sensitive test is almost certainly a thorough and methodological visual examination of the surface of the oral mucosa. However, the true sensitivity of the identification of lesions which will go on to malignant disease is unknown. White patches, red patches and ulcers can be identified by trained paramedics with high sensitivity but the proportion of these which have the potential to turn malignant is unknown.

This criterion is not fulfilled at present.

VI. *Are the tests acceptable to the population?*

Examination of the mouth by a dental specialist is perhaps the most acceptable of all screening tests proposed for cancer.

This criterion appears to be fulfilled.

VII. *Is the natural history of oral cancer known?*

It is obvious that malignant lesions begin small and grow over time. However, very little is known about the natural history of oral cancer and it is not known how long it takes for a lesion to develop to a stage when it may be incurable. Smaller lesions may not necessarily be early in a chronological sense. The main determinants of survival, however, in individual cases appear to relate to the size and degree of local or distant spread of the primary tumour. An increase in size of a lesion from less than 2 cm to between 2 and 4 cm results in a change from stage I to stage II disease and reduces 5-year survival by around one third.

This criterion is not fulfilled.

VIII. *Is there a strategy for determining which patients should and should not be treated?*

Certainly for pre-malignant lesions there is no general consensus on treatment policy.

This criterion does not appear to be fulfilled.

IX. *Is the cost of screening acceptable?*

The cost of an oral examination is low in itself. The cost of further investigation of false positives is an unknown variable and certainly the proportion of false positives is not known.

There is insufficient information available to evaluate this criterion.

X. *Is effective treatment available and does management of cases in the early stages have a favourable impact on prognosis?*

There are surprisingly few data available regarding the prognostic advantage of early detection of precancerous

lesions. It would seem intuitive that regular observation of patients with such lesions should result in early detection of any malignant change. As stated previously, an increase in the size of a lesion <2 cm to between 2 and 4 cm results in a change from stage I to stage II disease and reduces 5-year survival by one third. The lead time (bias) introduced by screening is unknown at the present time. It is not clear that the apparent survival advantage of follow-up and early detection is greater than the lead time bias.

This criterion is probably fulfilled.

In summary, therefore, while the mouth is an ideal target for screening programmes due to its accessibility, there is no evidence to support population screening for oral cancer at the present time. There is no data available regarding whether oral cancer screening can lead to a reduction in mortality from oral cancer. Many of the criteria of Wilson and Junger are fulfilled. However, there are notable weaknesses in our knowledge, principally in that the natural history of early lesions and most "premalignant" lesions is unknown. Based on this uncertainty, and the lack of knowledge even on the sensitivity and specificity of the screening test, it is difficult even to recommend the need for randomised trials of oral cancer screening. Better tests need to be developed, more basic research on the natural history of oral cancer needs to be undertaken and the sensitivity and specificity of present and "new" tests needs to be done. Only then could a decision be taken regarding the establishment of randomised trials.

RECOMMENDATIONS OF AREAS FOR FURTHER RESEARCH WORK

A summary of the areas requiring further research work are given in Table 1.

Oral cancer epidemiology

The Advisory Group identified several areas of oral cancer epidemiology requiring further research. These included work on the natural history of oral cancer, since presently little information was available on, for example, the number of oral cancers arising from an identifiable premalignant lesion such as leukoplakia, or of the risk of malignancy in an existing leukoplakia. The epidemiology of potentially premalignant lesions is currently not well understood and should be a priority for further research.

Table 1. Recommendations of areas for further research work

1. The natural history of oral cancer.
2. The epidemiology of potentially malignant lesions.
3. Epidemiological studies to investigate causes of currently increasing incidence rates.
4. The aetiology of oral cancer in non-smokers/non-drinkers.
5. Genetic factors in oral cancer.
6. Further defining the particular aspects of diet which may reduce the risk of oral cancer.
7. Identification of chemoprevention agents for use in trials of prevention of second primary tumours, and in patients at high risk of oral cancer, i.e. with potentially premalignant lesions.
8. The treatment of potentially malignant lesions, e.g. leukoplakia.
9. Chemotherapy in the treatment of oral cancer.
10. Examination of patient outcomes according to treatment centre and regimes.
11. Evaluation of post-treatment quality of life, including aesthetic, nutritional and functional.
12. The identification of biomarkers for use in future treatment and chemoprevention studies.

In view of the current increasing incidence of oral cavity cancers in Europe, it will be important to understand why the disease is becoming more common. In particular, whether this is due to the same factor in all countries, is caused by one or several factors, and whether it is caused by traditional risk factors such as alcohol and tobacco or alternative risk factors. In this respect the Advisory Group recommends that epidemiological studies designed to address these issues include the following areas for research: the role of viruses in the aetiology of oral cancer, particularly human papillomavirus and herpes simplex virus; the role of genetic factors; and the collection of information on current and past use of mouthwash in European countries. Little is also known about the aetiology of the disease arising in non-smokers/non-drinkers and regarding the importance of known aetiological factors for tumours at individual subsites within the oral cavity.

Finally, with information collected to date by epidemiological studies suggesting protective effects of some dietary elements research should continue in this field since results would have particular relevance not only to recommendations for reducing the risk of disease but also possibly for future chemoprevention studies.

Chemoprevention of oral cancer

At present dietary supplementation with vitamins and minerals could not be recommended by the Advisory Group for the primary prevention of oral cancer, and further research on chemoprevention is needed. It was considered that this area of research deserves more attention particularly with respect to (1) the treatment of potentially premalignant lesions, and (2) previously treated oral cancer patients to reduce the risk of a second primary tumour in the upper aerodigestive tract. Such agents as N-acetyl cysteine and retinoids are of particular interest and future studies would ideally integrate the use of biomarkers enabling the consideration of intermediate endpoints.

Oral cancer screening

Screening for oral cancer could not be recommended by the Advisory Group at the present time, either on a population or on a trial basis. This is primarily due to lack of knowledge about the natural history of the disease and consequently the unknown specificity and sensitivity of screening tests such as visual oral examination.

Laboratory research

A particularly important area for future laboratory research would be the identification of biomarkers for use in future treatment and chemoprevention studies. At present promising candidates have been identified such as cytokeratines, retinoic acid binding proteins and micro-nuclei assays.

Continuing research identifying metabolic factors associated with alcohol and tobacco would also continue to be of interest in order to identify individuals at higher risk of oral cancer associated with exposure to these factors.

Education and training needs

The Advisory Group consider it important that training was available, particularly amongst medical students and junior doctors, in the conduct of a routine oral examination and the identification of lesions requiring referral to a specialist in oral disease. This training should be given by qualified oral medicine professionals.

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