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Editorial

Chemoprevention and Oral Cancer—(More) Trials and (More) Tribulations

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WHILE EPIDEMIOLOGICAL studies have suggested a beneficial role for the intake of fruits and vegetables in the aetiology of several important forms of cancer, this protective effect has not been related so far to any single family of fruits and vegetables and the exact molecule(s) responsible for these effects is unknown [1]. While eating more fruits and vegetables should reduce overall cancer risk, it is logistically difficult to think of conducting a trial which randomises individuals into two groups, one of which has a fixed additional amount of fruits and vegetables added to their daily diet. It would, of course, be a tremendous achievement to identify the responsible elements in fruits and vegetables which confer this protection and to introduce them to the diet of the entire population in some form, be it pills, added to water supply, in bread or whatever.

The demonstration of a reduction in mortality in a randomised, controlled trial of chemoprevention in a recent study in China is of considerable significance [2]. The finding of a reduction in cancer mortality, especially cancer of the oesophagus and stomach, among those receiving supplementation with a group of antioxidants, beta carotene, vitamin E and selenium is the first intervention study which has demonstrated a reduced rate of death from all causes among the group receiving supplementation and a reduced death rate from total cancer and stomach cancer in particular. In many respects, chemoprevention has come of age although it must be borne in mind that this is, of course, a special population with high cancer rates and a long history of low dietary intakes of several important micronutrients. The results from this population at a dietary extreme cannot be directly applied to most western populations where the diet is generally much richer in essential micronutrients. It is likely that in such a population as the latter it would take a much larger number of study participants to detect a significant reduction which may also be smaller in size. However, these findings do provide another important element to the role of antioxidants in cancer in general and should serve to stimulate both basic research and research in molecular epidemiology in this area.

There was a reduced number of cases of prostate and colorectal cancer found among Finnish smokers randomised to alpha-tocopherol [3]: the approximate relative risk appears to be 0.66 for prostate cancer and 0.87 for colorectal cancer. However, a randomised controlled trial of beta-carotene and vitamins C and E involving 864 patients randomised to one of four treatment arms, who underwent colonoscopy for polyp identification after 1 year and 4 years, reported no evidence that either beta-carotene or vitamins C and E reduced the incidence of adenomas [4].

Non-steroidal anti-inflammatory drugs (NSAIDS) have recently been implicated as potential protective agents against colorectal cancer and adenomatous polyps. Initial anecdotal reports noting regression of adenomas in patients with familial adenomatous polyps have been followed by substantial epidemiological studies. There is a general level of agreement in the finding of a protective effect from such studies. There are randomised trials of familial adenomatous polyps demonstrating the regression of adenomas by NSAIDS [5]. In laboratory rodents, piroxicam, sulindac and aspirin all have been shown to reduce the frequency of development of colorectal neoplasia [6]. The mechanism of any effect remains obscure as does the dose required, and after the initial optimism generated by data from retrospective studies, it is disappointing that the results of a randomised intervention trial of low-dose aspirin in United States Physicians were null [7]. However, there is a very good case for a controlled trial of NSAIDS, probably using aspirin, in the prevention of colorectal cancer [8].

The mouth may represent a paradigm for chemoprevention. The high recurrence rates of potentially malignant oral lesions [9] and the occurrence of second primary neoplasms in one third or more of patients with oral carcinoma [10] beg the question as to the possibilities of reducing exposure to carcinogens such as tobacco and alcohol, and of the use of systemic medication that might modulate epithelial cell biology in such a way as to halt the progression in carcinogenesis.

In this issue of *Oral Oncology*, two reviews, one from the United Kingdom and one from Japan, provide comprehensive overviews of the current state of development of the field of chemoprevention although it is worthwhile to consider other findings such as those outlined above.

Hope of success has appeared in the recent comment on the progress of the EUROSCAN project [11]. Most important, however, are the results of a multicentre double-blind randomised study on the use of *etretinate* for the prevention of

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second primary tumours in patients with squamous carcinoma of the oral cavity or oropharynx [12]. This trial, carried out under the auspices of the French Study Group on Head and Neck Tumours (GETTEC), included 316 patients assigned to receive orally for 24 months, either etretinate 25 mg/day (after a loading dose of 50 mg/day for 1 month) or placebo, after surgery and/or radiotherapy treatment for the primary lesion. The results showed no differences in either the 5-year survival rate or in the disease-free survival rate. Despite the fact that the study design and patient compliance could be criticised [13], these disappointing findings, together with problems related to toxicity and the need to persist with the use of other chemopreventive agents that have been shown to be effective in order to maintain their protective effect, present serious challenges.

Long-term studies are obviously necessary if research on intervention is to make progress: at present each advance is swiftly followed by a disappointment. Of course, if there were readily available intermediate end-points available studies could be smaller and shorter. However, in the absence of such end-points, large studies lasting for many years are needed to investigate the efficacy of different intervention strategies. There are many difficulties in conducting such studies and organising them. The logistics of following 30 000 individuals as in China [2], supplying them with drugs, monitoring compliance and side-effects, verifying end-points and follow-up are horrendous. Perhaps the greatest obstacle to conducting such studies lies in the ability to secure long-term financial support. Granting agencies are extremely reluctant to commit themselves to expensive and long-term support for individual research projects. This will be a factor limiting quick progress in this area: a reasonable level of funding and good organisation can help overcome the logistical hurdles.

1. Steinmetz KA, Potter JD. Vegetables, fruits and cancer. *Cancer Causes Control* 1991, **2**, 325–357.
2. Blot WJ, Li J-Y, Taylor P, *et al.* Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993, **85**, 1483–1492.
3. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of Vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994, **330**, 1029–1035.
4. Greenberg ER, Baron JA, Tosteson TD, *et al.* A clinical trial of antioxidant vitamins to prevent colorectal cancer. *New Engl J Med* 1994, **331**, 141–147.
5. Labayle D, Fischer D, Viel R, *et al.* Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 1991, **101**, 307–311.
6. Skinner SA, Penny AG, O'Brien PE. Sulindac inhibits the rate of growth and appearance of colon tumours in rats. *Arch Surg* 1991, **126**, 1094–1096.
7. Gann PH, Manson J, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumours in a randomised trial. *J Natl Cancer Inst* 1993, **85**, 1220–1224.
8. Farmer KC, Goulston K, Macrae F. Aspirin and non-steroidal anti-inflammatory drugs in the chemoprevention of colorectal cancer. *Med J Australia* 1993, **159**, 649–650.
9. Shklar G. Modern studies and concepts of leukoplakia in the mouth. *J Dermatol Surg Oncol* 1981, **7**, 996–1003.
10. Lippman SM, Hong WK. Second malignant tumours in head and neck squamous cell carcinoma: the overshadowing threat for patients with early stage disease. *Int J Radiat Oncol Biol Phys* 1989, **17**, 691–694.
11. De Vries N, Pastorino U, Van Zandwijk N. Chemoprevention of second primary tumours in head and neck cancer in Europe: EUROSCAN. *Oral Oncol, Eur J Cancer* 1994, **30B**, 367–368.
12. Bolla M, Lefur R, Ton Van J, *et al.* Prevention of second primary tumours with etretinate in squamous cell carcinoma of the oral cavity and oropharynx. Results of a multi-centric, double-blind randomised trial. *Eur J Cancer* 1994, **30A**, 767–772.
13. Benner SE, Lippman SM, Hong WK. Chemoprevention of second primary tumours: a model for intervention trials. *Eur J Cancer* 1994, **30**, 727–729.

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