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EDITORIAL

Chemoprevention of cancer

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"Hee is a better physician that keepes diseases off us, than hee that cures them being on us. Prevention is so much better than healing, because it saves us the labor of being sick". *Thomas Adams, 17th century.*

Prevention of a disease is undoubtedly the best approach to its control. However, the importance of identifying effective measures to prevent human cancers has only received ample attention during the last 30 yrs [1]. The current effort in this field involves two major areas. One area, which is fairly well-established, involves investigation of environmental and lifestyle factors, that could be changed in order to reduce subsequent risks of developing cancer. The other comparatively recent approach [2], is chemoprevention, which refers to intervention with chemical agents, either natural or synthetic, which can inhibit or reverse the carcinogenic process. In 1982, the chemoprevention programme was established at the National Cancer Institute (NCI). This programme tried to integrate the results from preclinical studies, and to identify possible cancer-inhibiting agents for testing in human chemoprevention trials [3]. In the nineties, the opportunities for making advances in this field are rapidly growing, as a result of basic research discoveries. Molecular changes associated with cancer risk are increasingly accessible for study, and some of these findings will almost certainly lead to ways of reducing cancer incidence [4]. Clearly, one of the top priorities in cancer prevention remains elimination of known carcinogens, the most important of which is tobacco [5]. However, complete elimination of carcinogens is not likely to be socially-acceptable or achievable. Therefore, other strategies must also be developed and applied.

Carcinogenesis

To appreciate the potential impact of chemopreventive strategies, an understanding of the aetiology of malignancy is necessary. A detailed discussion of carcinogenesis is beyond the scope of an introduction; therefore, only a brief summary of the most important concepts will be presented. Carcinogenesis induced by chemicals involves the separate and independent (multistep) processes of tumour initiation, tumour promotion and progression. The initiation step, involving changes at the genetic level, is followed by several promotion and progression steps to frank malignancy [6, 7]. A key feature is continued growth or replication of the abnormal cells, which is necessary, not only for their expansion, but also for the generation of new, potentially "more malignant" properties, by the acquisition of additional inheritable changes in the developing clone(s). The multistep nature of the carcinogenic process raises the possibility of intervention at different stages [4]. Intervention at the initiation stage involves approaches such as elimination of carcinogens, or interference with the activation of precarcinogens to active carcinogens. Again, it has to be stressed that it is not easy to eliminate risk factors, even if they are known. This is especially true for risk factors resulting from our lifestyle, considering that millions of smokers still constitute the largest body of volunteers in the epidemiology of lung cancer. The discussion on abandoning smoking is often clouded by the argument that the majority of heavy smokers will never acquire lung cancer. This points to the interindividual variability in susceptibility to carcinogens, and there are several lines of evidence that metabolic factors are involved in such variability [8, 9]. Metabolism of carcinogens, and also the subsequent steps of carcinogenesis, are affected by host factors and governed by the balance between opposite forces, such as metabolic activation and detoxification, formation and scavenging of radicals, and deoxyribonucleic (DNA) damage and repair. Another important concept in chemoprevention is the "field defect" or "field cancerization" model. This concept proposes a basic pathogenetic mechanism that links the primary epithelial carcinogenic process to the development of second primary tumours in the head and neck, oesophagus and lung, either simultaneously (synchronous), or in a temporal sequence (metachronous) [10, 11].

Field cancerization provides a sensible model for aerodigestive tract carcinogenesis and a basis for chemoprevention studies. It explains the extensive molecular, biochemical, and histological changes, which occur in individuals with significant carcinogen exposure. In addition, patients at high risk for cancer are identified, providing a population likely to benefit from chemoprevention studies.

Inhibition of carcinogenesis

Extensive studies in experimental animals and in humans, provide evidence that dietary factors play an important role in cancer causation [12, 13]. The early studies in animals were conducted as a result of clinical

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and epidemiological observations in humans [12]. The, sometimes dramatic, geographic and ecological variations in cancer patterns, as well as the changing incidence of cancer in migrants, have pointed to differential exposures in human populations. Dietary factors probably play a prominent role in explaining these differing cancer rate [13].

In recent years, a variety of micronutrients has been identified as having the potential to decrease human cancer risk, including retinol, β-carotene, synthetic retinoids, vitamin E, folic acid, vitamin C, and the trace element, selenium. It is important to emphasize that there is a lack of consistency in some of the correlations found, with some epidemiological studies, reporting an effect on cancer incidence, but others being unable to demonstrate this [14, 15].

It is apparent that the human diet is varied and complex and cannot be easily assessed. The accuracy of information collected by dietary interview is not only limited by the human capacity for recall, but also by the complex methodology of dietary questionnaires. Diet records are laborious to maintain, and can only be collected on a limited number of individuals over a brief period of time.

Estimation of levels of micronutrients in biological samples provide objective measurements. However, their relevance to eating habits is not always clear. Moreover, samples have generally been obtained at one point in time. For many nutrients, little or no data are available regarding the relationship of a single biological measurement of one micronutrient level to long-term nutrient status, or to the carcinogenic process. It may also be theorized that the outcome of measurement of a potential dietary preventive agent in cancer patients may rather be a reflection of the disease on that agent [16]. Thus, abnormal levels should be interpreted with caution, and the definite tests of dietary preventive agents should be conducted under controlled conditions, where the agent serves as the only variable between the treated and control groups.

Unique aspects of chemoprevention

In addition to naturally occurring compounds present in food, a number of synthetic compounds have been shown to slow or to modify the carcinogenic process in animal models. This has led to the introduction of a strategic approach by the NCI, selecting promising chemopreventive agents by using standard batteries of *in vitro*, *in vivo* and toxicological assays [17]. Among the new agents selected in this way are: N-acetylcysteine glycyrrhetinic acid, oltipraz and ibuprofen [18].

In contrast to cancer chemotherapeutic agents causing major toxicities but considered acceptable in patients with established malignancy, the optimal chemopreventive agent should have little, or preferably no, toxicity at all. And it is important that, before initiating trials evaluating the efficacy of a potential chemopreventive agent, that this agent is carefully tested in the laboratory and clinic. Also, potential dietary preventive agents must be considered as chemical compounds, even though their presence in the human diet has led to their recognition.

Cancer prevention trials have three unique areas that should be considered when evaluating a new potential preventive agent:

1. The target population consists of cancer-free individuals, often with a higher statistical risk for developing cancer but otherwise healthy.
2. The degree and frequency of side-effects, both acceptable to the individual and medically and ethically justifiable, differs from those in "patients". If the target population indeed includes patients, for instance those who were treated for a first cancer and are now at risk for a second primary tumour (SPT), more expressed toxicity seems acceptable [19, 20].
3. Chemopreventive agents will have to be taken for prolonged periods, probably even life-long.

Many naturally occurring, as well as synthetic, compounds have shown chemopreventive activities. Some of these agents are thought to be free of side-effects, whereas others are clearly toxic. The decision to conduct clinical trials should, therefore, be made on an agent-by-agent basis, driven by the concern for side-effects [21].

Clinical trials in chemoprevention

Already, over 30 clinical trials have been registered as either completed, in progress, or in the planning stages [3]. The organ sites include the lung and the upper aerodigestive tract and, recently, HONG *et al.* [19] reported an encouraging positive result using 13-*cis*-retinoic acid to inhibit the development of SPTs of the head and neck. In this study, in which 103 patients were entered, only two (4%) second tumours occurred in the "13-*cis*" group, as compared to 12 (24%) in the placebo group. These data showed, for the first time, that chemoprevention of SPTs was possible. However, the number of patients in this trial was small and the number of SPTs in the placebo group (24%) exceptionally high (5–10% are expected after 32 months), whereas the number of SPTs in the intervention group (4%) was very low. Moreover, the toxicity of 13-*cis*-retinoic acid, at a dose of 50–100 $mg \cdot cm^{-2}$ was considerable. Thus, there is a need to confirm these results by other investigators. Currently, efforts are underway to evaluate 13-*cis*-retinoic acid at a lower dose (30 $mg \cdot m^{-2}$). In Milan, a similar study was initiated in 1984, in curatively-treated lung cancer patients, using natural vitamin A (retinol palmitate). A recent analysis showed that the differences in favour of vitamin A are almost reaching statistical significance [22], only 4 out of 150 of the vitamin A-treated patients had to stop the drug due to toxicity [23].

The European Organization for Research and Treatment of Cancer (EORTC) is now performing a large trial based on this experience, called the Euroscan trial [20]. This European-wide study will also test for SPTs in 2,000 patients successfully treated for lung and head and neck cancer. The Euroscan trial uses a factorial design with the following intervention groups: retinol palmitate, N-acetylcysteine, both agents, or no treatment. N-acetylcysteine, initially tested by DE FLORA *et al.* [24],

recently successfully passed the NCI screening. The drug has attracted attention as an early stage inhibitor, already extensively used in patients with chronic obstructive pulmonary disease, with minimal toxicity [25].

Intervention studies are time-consuming, require a large number of subjects, and thus are expensive to conduct. The final end-point, cancer, especially in primary prevention studies, could take more than 10 yrs. Therefore, endpoints other than the occurrence of cancer may be appropriate, and several investigators have tried to identify biological markers which might be used to directly measure the impact of a certain intervention on carcinogenesis [26]. This approach would allow chemoprevention trials to be much shorter in duration. So far, the most widely-used markers are micronuclei (fragments of extranuclear DNA), which represent ongoing DNA damage and histological changes (metaplasia). Recently, molecular markers such as DNA-adducts have been introduced into the laboratory [27].

Thus, for future trials, it is strongly advised not simply to address the effect of the intervention on tumour incidence, but also to investigate the molecular and biochemical changes which accompany the multistep process of carcinogenesis.

Conclusion

Chemoprevention has developed from an interesting theoretical model into a realistic adjuvant treatment. Increased understanding of the biology of carcinogenesis will most probably lead to new approaches, and the concepts and methods that have been developed in the field of cellular and molecular biology, will certainly accelerate this progress. Finally, well-designed, large-scale, randomized trials are critical for the advancement our knowledge concerning promising cancer chemopreventive agents.

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