Chemoprevention of cancer: a controversial and instructive story

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Increased intake of fruits and vegetables seems to be one of the simplest means of decreasing the risk for cancer. Cancer-preventive effects of fruits and vegetables have been observed in epidemiological studies, which could not, however, distinguish the effects of the various ingredients. Antioxidant defence has been proposed as a mechanism of chemoprevention, although inconclusive results have been obtained. The results of randomized intervention trials have shown that β-carotene supplements are of limited value and may even be deleterious. Vitamins are a good marker of the ingestion of fruits and vegetables, and vitamin E (α-tocopherol) is a lipid-soluble antioxidant which can scavenge free radicals. It had no significant effect on the risk for lung cancer of long-term smokers in an intervention trial, but it decreased both the incidence of and mortality from prostate cancer; however, there was a 50% increase in the occurrence of cerebral haemorrhage among the men given vitamin E. Aspirin and aspirin-like drugs appear to decrease the risk for intestinal tumours; the mechanism of action appears to involve diminishing prostaglandin production due to inhibition of cyclooxygenases. Dietary fibre has been linked to a reduced risk for colorectal cancer in many observational studies, but opposite findings were reported recently. In order to resolve these paradoxes, we need to understand better the underlying biology, develop mechanistic hypotheses and test them in clinical trials in humans. Until that time, we should confine any premature enthusiasm for chemopreventive micronutrient supplementation.

Humans are exposed to a large array of carcinogenic insults, from endogenous and xenobiotic carcinogens to radiation, physical agents and viruses. In general, the term cancer prevention is used to refer to the prevention of exposure to carcinogens, in the expectation that this will eventually lead to a reduction in cancer incidence. Chemoprevention, however, may offer an opportunity for more immediate results, especially in subjects known to be at high risk for cancer. There is still some disagreement about what constitutes a chemopreventative agent. For instance, hundreds of observational studies have shown that persons...
Micronutrients in health and disease

who consume more fruit and vegetables have a reduced risk of cancer than those who consume less or none. There is considerable evidence that many chemicals present in the diet at only low concentrations play an important role in protecting people against cancer. Some micronutrients, defined as nutrients present in the body in amounts less than 0.005% of body weight, have been suggested to protect against cancer; these include β-carotene, α-tocopherol and ascorbic acid. Many people prefer prescription of pills to proscription of harmful lifestyles, despite the fact that some pills, e.g. vitamin supplementation, have shown little evidence of any benefit. So, although the evidence indicates that modification of food patterns can lower cancer risk (cancer prevention), researchers continue to search for easy-to-take, prepackaged natural or synthetic compounds (chemoprevention).

Putative chemopreventive agents are generally agreed to include pharmaceutical drugs (such as aspirin and aspirin-like drugs), micronutrients, certain food constituents and hormonally active agents. The International Agency for Research on Cancer began a series of Handbooks of Cancer Prevention in 1997 by considering the cancer-preventive activity of non-steroidal anti-inflammatory drugs (NSAIDs)\(^1\). Subsequent volumes have been published on carotenoids\(^2\), vitamin A and retinoids\(^3\).

**Biological basis of chemoprevention: importance of mechanisms**

Mechanistic studies of carcinogenesis have revealed possibilities for intervention by preventive agents. The classical view of experimental carcinogenesis is that tumour initiation is followed by tumour promotion and progression in a sequential fashion; however, while each stage of experimental carcinogenesis appears to be involved in humans, the temporal nature of initiation, promotion and progression in human cancer is complex. Thus, the use of mechanistic data in identifying and evaluating chemopreventive agents can increase confidence in assessments of causality. Although many chemopreventive agents have been proposed empirically, recent advances in the molecular biology of carcinogenesis suggest that new and better agents will be developed\(^4\). In the following, the inflammatory process, which is linked to carcinogenesis in many instances, is discussed from the point of view of mechanistic aspects of cancer chemoprevention.

One important aspect of tumour development is the release of arachidonic acid and its metabolism to eicosanoids, including prostaglandins\(^5,6\). An expanding body of evidence indicates that down-regulation of the
Cyclooxygenases (COX-1 and COX-2) will be an important strategy for preventing cancer, because cyclo-oxygenases catalyse the formation of prostaglandins, which have multiple effects that favour carcinogenesis. A number of prostaglandin synthesis inhibitors are effective in counteracting tumorigenesis. Compounds such as anti-inflammatory steroids (i.e. glucocorticoids) are potent inhibitors of experimental skin carcinogenesis. These compounds are effective inhibitors of phospholipase A2, which may explain their ability to decrease the amount of arachidonic acid available for metabolism for pro-inflammatory prostaglandins. Vitamin E can also inhibit production of prostaglandins by inhibiting phospholipase A2 activity.

Aspirin and aspirin-like NSAIDs can inhibit colorectal tumorigenesis and are among the few agents reported to be useful for chemoprevention of neoplasia. The cyclo-oxygenase pathway is a major target for prevention by NSAIDs, primarily because an inducible cyclo-oxygenase (COX-2) plays a role in inflammation as well as in apoptosis and cellular adhesion in some cells. From the perspective of chemoprevention, the recent finding that over-expression of the gene for COX-2, a key enzyme for the formation of prostaglandins from arachidonic acid, is an early and central event in colon carcinogenesis provides an important target for the development of chemopreventive agents. Over-expression of COX-2 in epithelial cells inhibits apoptosis and increases the invasiveness of tumour cells. Treatment of colon tumour cells with NSAIDs results in a dramatic increase in arachidonic acid concentration, which, in turn, stimulates the conversion of sphingomyelin to ceramide, a known mediator of apoptosis. Aspirin and salicylate have recently been shown to inhibit NF-kB activation, which, in turn, may contribute to their ability to increase apoptosis.

An alternative explanation for the efficacy of NSAIDs in the prevention of colorectal cancer is their ability to scavenge reactive oxygen species. Reactive oxygen species such as superoxide anion, hydroxyl radical and non-radical hydrogen peroxide may be involved in a range of human diseases, such as inflammatory bowel disease, colorectal cancer and rheumatoid arthritis. Accumulation of reactive oxygen species in response to inflammatory conditions or exposure to environmental conditions that generate these species can both initiate and promote cancers by damaging critical macromolecules such as DNA, proteins and lipids, and by acting as cell-signalling molecules. Antioxidants – such as ascorbic acid, α-tocopherol, β-carotene and several polyphenolic compounds found in green tea and fruits and vegetables – have been reported to have chemopreventive activity in experimental animal models. Micronutrient deficiency not only causes symptoms of severe deficiency but may also have more subtle effects on tissue function, including changes in immunosurveillance and antioxidant capability.
Micronutrients in health and disease

Human intervention trials: a gold standard?

Since 1970, the role of dietary fibre in colorectal cancer has been explored in many case-control studies, with relatively consistent results suggesting a reduced risk with higher consumption. A meta-analysis of these studies showed both an inverse association and a dose-response relationship\textsuperscript{14}. The results of the cohort studies have been much less convincing. In a recent prospective study of almost 90,000 female nurses who were followed-up for more than 16 years, colorectal cancer developed in 787 women, and neither total dietary fibre nor dietary fibre from vegetables, fruit and cereals separately was associated with the risk for distal colonic or rectal adenomas. In fact, greater consumption of vegetable fibre was associated with a small increase in risk\textsuperscript{15}.

Is this a unique paradox? Not at all. The transformation of dietary data collected by means of questionnaires into actual nutrient intake entails numerous problems. How accurately can foods be measured? How accurate is the database, both in its catalogue of relevant foods and in its imputation of fibre content? Should we be looking at specific kinds of fibre rather than treating a very heterogeneous mixture as a single variable? How does fibre work? Still other questions involve the essential nature of epidemiological studies. Case-control studies suffer from problems of selection bias, the crucial bias being the absence of patients who do not survive long enough to enter the study. There is also potential bias due to differences in recall of diet between patients with disease and controls. Although comparisons made within cohorts are relatively unbiased, the cohorts themselves may be unrepresentative of the general population because specific populations are targeted for recruitment and there is a degree of subsequent self-selection into a cohort. This recruited population may differ from the general population in terms of the behaviour under study and in terms of clustering of other causal and protective factors. Nevertheless, cohort studies are considered to be less prone to bias than the case-control approach in epidemiology.

Both case-control and cohort studies have tended to show a reduced risk for colorectal cancer after sustained aspirin use\textsuperscript{16}. Of 15 observational epidemiological studies that specifically addressed the association between regular use of aspirin and/or NSAIDs and colorectal cancer, nine case-control and five out of six cohort studies found a lower risk for colorectal cancer; one cohort study showed an increased risk for colorectal cancer among users of NSAIDs\textsuperscript{10}.

As observational epidemiology studies can be subject to bias, there is concern that chemoprevention with aspirin or NSAIDs should be recommended only if there is confirmatory evidence from an
Chemoprevention of cancer

intervention study in human patients. Although several such studies have been performed with aspirin, designed primarily to determine if this drug reduces the risk for heart disease, so far only one such trial has been conducted on the effect of aspirin use on colorectal cancer occurrence\textsuperscript{17}. In this study, aspirin prevented the occurrence of heart attacks; therefore, the experimental use of aspirin in the trial was stopped after 5 years. The participants in this trial have now been followed-up for the occurrence of colorectal cancer for up to 13 years. There is little or no evidence of a protective effect with regard to colorectal cancer, although there was some evidence of a reduction in incidence towards the end of the period of observation. The results of this trial, therefore, do not confirm the observational data.

From dietary observations to individual micronutrients: difficulties exemplified by β-carotene

A number of studies have been performed in which the serum concentrations of β-carotene have been related to subsequent cancer occurrence or dietary intake of β-carotene and assessed in observational epidemiological studies in relation to cancer risk\textsuperscript{18}. The results of these studies suggest that β-carotene has cancer-preventive effects against cancers of the lung, oral cavity and pharynx. In order to confirm this interpretation, three large intervention trials were started in the 1980s. Enthusiasm for use of β-carotene in chemoprevention was substantially dampened by the outcomes of these trials. In the two largest, β-carotene use significantly increased the risk for lung cancer among smokers and/or asbestos-exposed workers within 3–6 years after the start\textsuperscript{19–21}. The third trial, conducted among physicians in the US who were primarily non-smokers, showed no increase in the risk for lung cancer\textsuperscript{22}. In one of the trials, α-tocopherol supplementation had no effect on the occurrence of lung cancer, although men taking this drug had a significantly reduced risk for prostate cancer\textsuperscript{23}.

The results of observational epidemiological studies of β-carotene are thus in clear conflict with the results from randomized intervention trials. No clear-cut mechanistic explanation has been found to explain the findings of the intervention trials, and research has now switched to investigation of the interaction between the products of cigarette smoking and heavy exposure to asbestos and high blood concentrations of β-carotene. Use of β-carotene has been stopped in all of the on-going trials of chemoprevention except one.

The finding of a 32% reduction in the incidence of prostate cancer and a 41% reduction in deaths from this cancer among the smokers...
randomly assigned to a daily dose of α-tocopherol (vitamin E) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study is intriguing. There was, however, a 50% increase in the occurrence of cerebral haemorrhage among those men taking vitamin E\textsuperscript{23}. Thus, before use of vitamin E can be recommended for the prevention of prostate cancer, another trial should be conducted in an independent setting, with careful attention to the possible side-effects of vitamin E.

**Chemoprevention of cancer: where to now?**

There is an old Malayan proverb that goes: ‘Don’t think there are no crocodiles just because the waters are calm’. When it comes to micronutrients and cancer chemoprevention, the sense of assurance afforded by the results of observational epidemiological and experimental studies is often false and short-lived. Those who began to promote the use of micronutrient supplements on the basis of the results of the dietary observational studies saw only the untroubled surface and believed that supplements could be preventive. They were disappointed. In order to take further steps in understanding the roles of various potential chemopreventive agents, such as dietary fibre (and its components), plant foods and their constituents, complex carbohydrates and antioxidants, we need greater focus on experimental human biology and better data from intervention trials. Randomized intervention trials are needed to provide the required evidence for the efficacy and toxicity of rational chemopreventive strategies among ‘healthy’ asymptomatic people.

**References**