Current Strategies for Cancer Prevention: Chemoprevention

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Observations at ecological level show strong correlation between exogenous exposures, such as fat consumption, and risk of cancers. The correlations are less but significant at an individual level between many dietary items and cancer risk based on case-control and cohort studies. Most specific attempts to evaluate the role of diet on cancer risk stems from use of serum sample banks and estimation of different components of biochemistry in cases of cancer and healthy controls. The extension of this vast amount of epidemiological knowledge has resulted in preventive trials, chemoprevention of cancer, and in routine use of preventive substances, vitamins and minerals. However, the trials are relatively few and even less frequent are those with invasive cancer as end point. Furthermore, the results of these trials have been rather negative, and it seems at present that vitamins and minerals widely used in adult age for chemopreventive purposes are relative ineffective to prevent occurrence of invasive cancer or death from cancer. This does not imply that these chemical substances were not causes of cancer.

The basis for primary prevention of cancer is well established, because important causes of cancer are known. However, apart from reducing cigarette smoking, few easily applicable measures to decrease cancer incidence are available. Smoking has been estimated to cause about one third of cancer deaths in western countries.

Approaches to the prevention of cancer vary. Traditionally, the most common method has been health education on an individual or community basis via the mass media or by other channels. In several countries, other means have also been applied: legislative action (such as banning of advertisement), price regulation and policy decisions in relation to health services. A reduction in tobacco use has been the principal objective in most such actions. Other environmental changes have been attempted, for example, in the development of dietary policies and advice, the elimination or reduction of exposure to chemical carcinogens from the working and general environment, and the improvement of radiation protection.

Recently there is much interest in chemoprevention in cancer control. Chemoprevention involves intervening with vitamins, minerals or other chemicals with the aim of preventing cancer, or more broadly to reverse, suppress, or prevent the process of carcinogenesis.

Evaluation of preventive efforts is done mainly in terms of follow-up and monitoring for changes in the exposures, risk factors, believed responsible for cancer, or in terms of early markers of the carcinogenic process or occurrence of precancerous lesions as an end point. Much less is known about the relationship between the preventive intervention and the final outcome, cancer occurrence. International trends in lung cancer mortality, in particular, can be related to cohort-specific trends in smoking, particularly if allowance is made for the introduction of low-tar and filter cigarettes in the last 30 years. Studies of migrant populations are another well established method of demonstrating the effect which environmental change can play in the risk of cancer; however, the extent to which the change in cancer risk in migrants can be related to specific changes in their external or socio-cultural environment has not been ade-
Optimal in many ways to show the role of environmental exposures in the etiology of cancer is through use of biological sample banks collected in the past and linkage of the sample bank and a cancer registry. One of the largest studies was run in Finland, a bank of 40,000 serum samples established in late 1960’s by the Social Insurance Institution was linked with the Finnish Cancer Registry early 1980’s. More than 700 cancers with 1400 controls were analysed for several vitamins, trace elements, infections and tumour markers. Table 1 shows the risk of cancers among those with low levels (lowest quintile except three lowest quintiles for alpha-tocopherol for males) of retinol, beta-carotene, alpha-tocopherol and selenium. The relative risks for stomach cancer were high but also for breast and lung cancer there were associations with most of the biochemical substances studied. The risk of total cancer increased with the number of the substances with low level. The estimates for population etiologic fractions for dietary factors were close to the estimate of one third by Doll and Peto 1).

Worldwide there is a large consumption of chemopreventive agents, mainly vitamins and minerals. The scientific evidence on their effectiveness is limited, however. International Union against Cancer and several other international bodies have shown interest in chemoprevention in cancer control. The following is mainly based on the reviews of UICC, WHO and EU 2,3). Much of the problems in evaluation of cancer prevention in general 4) apply also to chemoprevention.

Buiatti et al 3), combined the information available on both published and on-going chemopreventive trials, which they were able to identify altogether 83 which were substantially more numerous than trials on diet (8 in number). Colon, lung, oral cavity and skin were the primary sites most often subjected to chemopreventive interventions. The agents commonly used in the intervention were beta-carotene, synthetic retinoids, calcium or several vitamins combined. Calcium was the agent for studies to reduce the risk of colon cancer or oesophageal cancer whereas the target primary sites were more wide spread in the vitamin trials.

Reduction in the occurrence of invasive primary cancers is the most convincing evidence on the effectiveness of prevention. Relatively few of the chemopreventive trials have the invasive disease as an end point. Typically, the large trials on lung, oesophageal and breast cancer have incidence of or mortality from invasive cancer as an outcome. Early markers of DNA damage, cell proliferation, mutagenicity etc. are common outcomes as well as occurrence or recurrence of precancerous lesions.

The first results of the large intervention studies were published from the alpha-tocopherol, beta-carotene lung cancer intervention trial (ATBC study) carried out in Finland by the National Public Health Institute 5,6). About 29000 male smokers were randomized into both alpha-tocopherol and beta-carotene, alpha-tocopherol only, beta-carotene only and placebo only arms. There was no protective effect of alpha-tocopherol nor beta-carotene on lung cancer or total cancer (Table 2). In fact, the numbers of new cases and deaths from cancer were somewhat larger in the beta-carotene group than in the placebo group. Essentially similar results were derived from large U.S. studies 7,8).

The only positive result of chemoprevention to reduce risk of invasive cancer is the reduced incidence of contralateral breast cancer among breast cancer patients with tamoxifen treatment 9). There is going on international breast cancer intervention study to find out the applicability of those results in healthy population and to quantitate the risks of the intervention.

Cost-effectiveness of chemoprevention is considered infrequently. Habbema et al 10) showed that only few life weeks would be gained per woman in average assuming a successful chemoprevention against colon cancer starting at middle age. The preventive treatment may be of duration of several decennia. Therefore, from several hundreds to more than one thousand years of chemopreventive treatment is needed to gain one life year. If the activity of chemoprevention itself or harmful effects of it will cause a marginally small decrease in quality of life, there will be a net loss instead of gain in the quality adjusted length of life.

Chemoprevention based on vitamins and minerals has not been shown to be effective so far. This does not imply that

Table 1. Smoking-adjusted relative risks of cancers at selected primary sites for low levels of biochemical substances (lowest quintile except three lowest quintiles for alpha-tocopherol among men): The Cancer Registry follow-up of the Social Insurance Institution Mobile Clinic Health Survey in Finland in 1968-1977 (14).

| Substance    | Lung men | Breast women | Stomach men | Prostate |
|--------------|----------|--------------|-------------|----------|
| Retinol      | 1.8      | 1.2          | 0.6         | 1.1      | 0.8      |
| Beta-carotene| 1.0      | 0.4          | 1.0         | 1.0      | 0.3      |
| Alpha-tocopherol | 1.1 | 1.1          | 2.5         | 2.2      | 1.7      |
| Selenium     | 1.8      | 3.1          | 6.7         | 2.0      | 0.8      |

Table 2. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study. Cancer incidence by intervention (5).

| Incidence cases of | Alpha-Tocopherol Yes | Alpha-Tocopherol No | Beta-Carotene Yes | Beta-Carotene No |
|--------------------|----------------------|---------------------|--------------------|------------------|
| Lung cancer        | 433                  | 443                 | 474                | 402              |
| Colorectal cancer  | 68                   | 81                  | 76                 | 73               |
| Stomach cancer     | 70                   | 56                  | 70                 | 56               |
| Total cancer       | 1129                 | 1162                | 1193               | 1098             |
nutrition, diet, vitamins, minerals or other biochemical substances were not causes of cancer. The most important reasons for the negative results of the well designed preventive experiments are probably related to the carcinogenic process, the biology of the disease. Cancer is a group of diseases which usually has a long latent period between first exposure and diagnosis. Where the risk factor in question acts late in the carcinogenic process, reduction in exposure might be expected to have relatively rapid effect. For example, risk of lung cancer declines quite rapidly towards levels found in nonsmokers within 15 years of smoking cessation. However, antioxidants presumably act to reduce DNA damage at relatively early in the carcinogenesis. Therefore, such an intervention should start early in life or to study early and intermediate outcomes. Both of these conditions result in other problems. If vitamins and minerals widely used as pharmaceutical products for chemopreventive purposes indeed are early stage carcinogens, the practice seems questionable to use them in adult age to prevent cancer death.

In many countries primary prevention is multifactorial. Tobacco-related legislation, price policy and food additives are examples on interventions in terms of regulative actions. Health education against smoking and to improve diet is common. Because the broad basis of the preventive activities, it is feasible to consider the trends and differentials of cancer risk at population level as indicators of the success of cancer control. Sir Richard Doll made a few years ago such a proposal and focused on young adults in his analysis. He emphasized that cancers among young adults have been produced in the near past by environmental factors (such as personal behaviour) whereas cancers occurring later in life are likely caused also by agents that existed many years before. Furthermore, prediction of future assumes examination of recent changes in the relatively young. Doll found that for many primary sites of cancer the mortality trends were the more favourable the younger was the age. Mortality reflects the influence of both the success in clinical activities and the success of prevention.

The Nordic countries have long term and accurate cancer registration. Decreasing trends in incidence were found in Finland for male lung cancer since 1970's which showed success of the anti-smoking policy in a country with long traditions and high prevalence of male cigarette smoking. Figures 1 and 2 show the very recent trends of both incidence and mortality for cancer of digestive organs. It was assumed that focusing on the recent trends in incidence also recent trends in causes could be established. The trends in incidence and mortality from total digestive cancer were decreasing in most age groups from 30 to 69 years. The changes were small but mainly according to the expectation, i.e. more substantial among the young, among women and in the last period (Figures 1 and 2).

In summary, it seems that research based on specific preventive trials has been rather negative as to indicate the potentials of prevention whereas more robust methods at ecological level give a more positive answer as to the effectiveness of primary

**Figure 1.** Age specific incidence and mortality rates of gastrointestinal cancer in Finland in 1980-84, 1985-89, 1990-94. Males.

**Figure 2.** Age specific incidence and mortality rates of gastrointestinal cancer in Finland in 1980-84, 1985-89, 1990-94. Females.
prevention in cancer control. However, little is known about the causes of changes in environment and life-styles at the population or individual level. Such changes may be due educational and regulatory efforts of health authorities and to growing health-consciousness among individuals. They may also be unrelated to deliberate health-based decisions, as when food fashions change or when purely commercial factors lead to the appearance or disappearance of certain products from the market.

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