Chemoprevention of Lung Cancer Is Proving Difficult and Frustrating, Requiring New Approaches

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The long-awaited results from EUROSCAN (i.e., the European Study on Chemoprevention With Vitamin A and N-Acetylcysteine), the randomized two-by-two factorial trial of vitamin A (retinyl palmitate) and N-acetylcysteine in patients with treated cancers of the lung or head and neck, show no benefit from either agent alone or from the combination. Among 2592 participants who received maximal tolerable doses for 2 years with a mean follow-up of 49 months, 916 experienced recurrence, second primary tumor, or death. The findings were analyzed exhaustively (1).

Hypothesis-driven chemoprevention of lung cancers, when put to the test of randomized large-scale clinical trials, so far has been disappointing, unlike important successes with selective estrogen receptor modulators for breast cancer and nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for familial colonic polyps. Once the carcinogenic processes have been initiated, prevention of cancers is much more difficult than one would like. The most reliable methods of reducing the incidence of cancers depend on avoidance of known carcinogenic agents, including UV radiation, tobacco, alcohol, various infectious agents, medical exposures to certain pharmaceuticals and hormones, ionizing radiation, and environmental and occupational exposures to a moderately long list of chemicals (2).

Working groups of the U.S. National Cancer Institute (NCI) have emphasized the importance of developing a solid scientific basis from mechanistic studies in vitro and in vivo to guide selection of potential chemopreventive agents and justify their use in phase I, II, and III trials. Priority should be given to population subgroups with particular host or environmental risk factors, including demonstrable genetic susceptibility to specific cancers, persons with precancerous lesions, and cancer patients at risk for second primary tumors. Clinically validated intermediate end points would be very useful; the aim is a reduction in the incidence of cancers, not just of precancerous lesions or biochemical responses.

Retinoids are among the most promising classes of chemopreventive agents. Their many proliferation-suppressing, differentiation-enhancing cellular effects and actions on specific receptor targets in the nucleus have given them an extraordinary laboratory basis for clinical testing (3). Retinoids have reduced tumor incidence and tumor mass and have extended tumor latency when animals were treated before, during, or—most importantly—after exposure to initiating and/or promoting agents.

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(4). The International Agency for Research on Cancer has recently published a series of four handbooks of cancer prevention, covering nonsteroidal anti-inflammatory drugs, carotenoids, vitamin A, and then nine specific retinoids (including all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, and 4-hydroxyphenyl retinamide) (3). Unfortunately, none of these retinoids appears to have a therapeutic index or a pattern of biologic responses suggesting better results than the vitamin A ester retinyl palmitate produced in EUROSCAN. Nevertheless, it is plausible that 13-cis-retinoic acid, 9-cis-retinoic acid, and even retinyl palmitate may be effective in yet-to-be-defined subgroups of patients. Retinoid X receptor-selective agents do have the advantage of avoiding teratogenic side effects.

Another rational approach to chemoprevention aims to increase detoxification of carcinogens by increasing conjugation with glutathione or glucuronides. Administration of the drug oltipraz, which enhances phase II metabolizing enzymes, including glutathione S-transferases, was used in trials to prevent primary hepatocellular carcinoma in China. Glucuronidation may be reversed by serum β-glucuronidase, which, in turn, may be inhibited by administration of D-glucaric acid [see (5)]. It is possible that these actions would be more relevant to early stages of carcinogenesis than to secondary prevention.

Lung cancer is a formidable foe. It is the leading cause of deaths due to cancers in both women and men. Treatment results are very disappointing in the majority of patients. The risk of lung cancer in former smokers does not fall upon cessation of smoking; it just stops increasing (thereby yielding a lower relative risk, compared with continuing smokers). Chemoprevention has yet to succeed, either in primary prevention in high-risk normal populations or in secondary prevention in patients with aerodigestive cancers. Primary prevention trials with α-tocopherol with or without β-carotene in the Alpha-Tocopherol, Beta-Carotene (ATBC) Trial in 29,133 smokers in Finland and with β-carotene plus retinyl palmitate in the Beta-Carotene and Retinol Efficacy Trial (CARET) in 18,254 smokers, former smokers, and asbestos-exposed workers in the United States found striking increases in lung cancer incidence, pointing to β-carotene as a potent human carcinogen (6,7). After inconsistent results from four much smaller secondary prevention trials [positive trials: references 16 and 17 cited in (1); no benefit trials: references 28 and 29 cited in (1)], EUROSCAN now shows no benefit from retinyl palmitate and/or N-acetylcycteine in a large number of patients with previously treated lung or head and neck cancer, of whom 93% were current or former smokers.

The strategy of relying on low-cost vitamins and existing pharmaceuticals as potential cancer chemoprevention agents reflects both the desire to have cost-effective approaches for the general population and the fact that prevention has had a much lower priority to date than therapy for investment by pharmaceutical companies and even by national agencies. We need successes in chemoprevention to build confidence that we have the capability not only to design or discover effective agents but also to recruit study populations in which to demonstrate their efficacy. Basically, we need “positive controls” for the testing of larger numbers of new agents, based on mechanisms, validated intermediate end points, variation in subgroups of the population, and cost-effectiveness in a cost-conscious health care environment. An agent deserving high priority is folic acid, which is definitely protective against neural tube defects early in pregnancy and probably protective against cardiovascular disease by reducing circulating homocysteine concentrations; since 1998, wheat grains have been fortified with folic acid. Folic acid is abundant in many of the same fruits and vegetables rich in carotenoids (5). One randomized study (8) found a significant reduction in sputum atypia in 73 longtime smokers given 10 mg folic acid plus 500 μg B12 for 4 months.

Despite the results to date, we should not be deterred. The overarching aim of the National Cancer Program is a reduction in the incidence and burden of cancers. Systematic discovery with microarray and proteomic methods of patterns of gene and protein expression in the surely very heterogeneous categories of cancers and in responses to pharmaceuticals, vaccines, and other agents may guide investigators to much more specific and effective interventions. An encouraging example is the report of two strikingly different patterns of expression in B-cell lymphoma, one of which is associated with a much more favorable response to chemotherapy (9). There can be little doubt that many more examples will follow. The Cancer Genome Anatomy Project of the NCI is stimulating such investigations.

References


