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EDITORIAL

Isn't Skin Cancer Preventable?

Frank L. Meyskens, Jr.*

What are the implications for cancer chemoprevention in humans as reported in the negative study by Tangrea et al. (1) in this issue of the Journal? Impeccably conducted, this multicenter, randomized clinical trial convincingly demonstrated that a low dose of isotretinoin did not decrease the appearance of new primary basal cell carcinomas in patients who had previously had two or more such malignancies and who had follow-up treatment for a mean duration of over 3 years. Using a similar study design, Greenberg et al. (2) demonstrated that beta carotene at a low dose also did not affect the natural history of skin cancer.

Generalization of the results from these investigations to the potential effectiveness of chemopreventive agents in cancer in general, or skin cancer specifically, is unwarranted for several reasons. A vast number of laboratory studies have established key features of cancer formation, or carcinogenesis: the process and its inhibition are carcinogen, inhibitor, dose, timing, tissue, and species specific (3). Translation of successful results in preclinical models into a positive outcome in humans may, therefore, not occur, even when a substantiated amount of positive data exists. Indeed, there is perhaps no preclinical model of carcinogenesis studied as extensively as that of the skin. Yet, the architecture of the normal skin of most lower mammalian animals (including the mouse and rat) and humans is very different and the histology of the skin cancers induced by chemical or UV light in lower animals is largely fibrosarcoma rather than the basal or squamous cell carcinoma typically seen in humans. Perhaps available preclinical model systems for cutaneous cancers are simply not relevant to the human disease and hence not predictive.

Many specific features of the current trial (1) require comment. What about the choice and dose of the agent? In well-designed trials, high doses of isotretinoin have been demonstrated to be effective in preventing new cancers in patients with xeroderma pigmentosum (4) and in patients with resected head and neck cancers (5). These results indicate that isotretinoin can function as a chemopreventive or chemosuppressive agent in humans, but the agent must be given at a high dose. Although a biological effect (as shown by the occurrence of side effects) from the isotretinoin was achieved in the study by Tangrea et al., the dose was low, about one-tenth of that used in the previously mentioned trials (4,5). It is unlikely that a higher dose of isotretinoin would be used in a subsequent trial because the

risk/benefit in the current study group of patients dictates a low ratio. However, in the trial by Greenberg et al. (2), use of a higher dose of beta carotene is well worth considering because the compound is safe and, in patients with erythropoietic protoporphyria, a photoprotective effect occurs only after a dose of 100 mg per day, and doses as large as 200 mg per day have been used safely in these patients for many years.

The issue of choosing the optimal dose for human chemopreventive studies is critical. For the next generation of large phase III chemopreventive trials, the choice of dose should be made from the results of smaller studies of intermediate markers in humans. With the use of rationally chosen intermediate end points for cancer therapy, modulation of these markers by the candidate chemopreventive agent should be measured (6). In the future, if a candidate chemopreventive agent cannot modulate a relevant intermediate marker in the tissue of interest in a population at risk or if the effectiveness of the agent falls below a dose at which the risk/benefit is too high, then the appropriateness of proceeding to a phase III trial will need to be carefully considered.

Another major difference between animal models of cancer and the human disease is that relatively high doses of the carcinogen are generally given over a short time period to normal animals, whereas low-dose exposure to multiple carcinogens is the usual case for humans. Preclinical carcinogenesis and chemopreventive models that more precisely simulate events that lead to human cancers are needed. Additionally, as noted by the authors of the current study, the population of patients with two prior basal cell cancers had a cutaneous environment that was clearly both heavily initiated and promoted. It is likely that only a high dose of isotretinoin, or of any other chemopreventive agent (2), would be effective in such a setting. Alternatively, a difference in the treatment and control curves may evolve only after a long follow-up, a situation which occurred for many end points in cardiovascular risk reduction trials.

The question of the risk/benefit ratio is a key one in prevention research (7). Considerable side effects to a chemopreventive agent may be quite acceptable in very high risk populations (e.g., patients with second visceral malignancies or hereditary cancer conditions), whereas few if any side effects will be tolerated in lower risk populations (e.g., patients with second cutaneous cancer or precancerous conditions).

Several alternative approaches to dose adjustments and the risk/benefit issue should also be considered. First, more effective chemopreventive agents with less toxicity need to be developed. Among the retinoids, fenretinide appears to have very few side effects and may well be nonteratogenic, a toxicity that precludes most retinoids from use in younger women. A large number of other nontoxic compounds with significant chemopreventive activity in animal models are now becoming available for clinical trial as well (8). Second, combinations of chemopreventive agents at low doses should be used. Extensive preclinical data indicate that individual agents are effective in combination at doses much lower than those of the individual

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compounds and at doses that are nontoxic. Although the regulatory issues in implementing trials of combinations of drugs (even if approved for other indications) are formidable, clinical and organizational strategies need to be developed to surmount this bureaucratic hurdle.

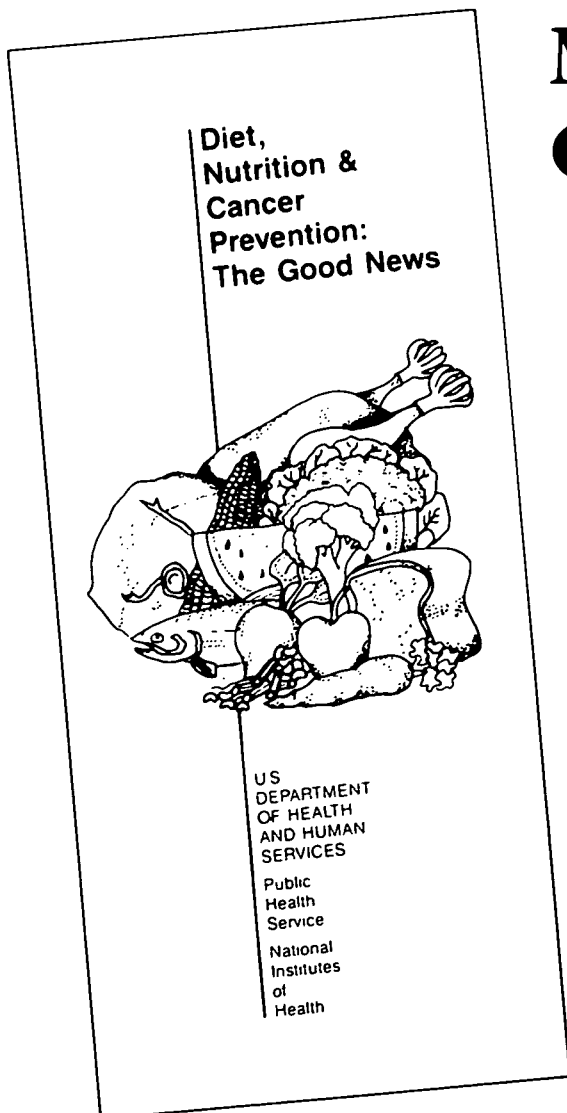
A large number of phase III clinical chemopreventive trials, planned and started in the mid 1980s and using a variety of natural and synthetic compounds, will come to fruition over the next 5 years. We now understand a great deal more about the design and conduct of such trials. We need to learn from the negative trials and to build on the positive ones as the science of carcinogenesis is translated first into the art and then into the science of cancer chemopreventive in humans (9).

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