Chemoprevention of Skin Cancer and Photoaging

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Abstract. Skin cancer and photoaging are thought to be the result of ultraviolet radiation exposure. “Chemoprevention” refers to the prevention of photoaging and skin cancer through the use of pharmacologic agents that inhibit or reverse the process of photoaging or carcinogenesis. As both carcinogenesis and photoaging are multi-step processes, tumor development may be halted at several prospective points of intervention. A wealth of research aimed at chemoprevention is emerging. In this article, a variety of potential chemopreventive agents are discussed, including vitamins, diet, aspirin and non-steroidal anti-inflammatory drugs, and topical agents. Although further studies are warranted to identify and determine the safety and efficacy of new chemotherapeutic agents, it is expected that both systemic and topical agents may soon be available that effectively prevent photoaging and skin cancer development.

Skin cancer and photoaging have been recognized to be the direct result of ultraviolet radiation exposure. Despite the depth of our understanding regarding the etiology of these conditions, interventional and cosmetic therapeutics are usually employed subsequent to the development of wrinkles and skin cancer, rather than as prophylactic measures before these conditions arise. Sun avoidance and sunscreens serve to block the initial step of photoaging and carcinogenesis, the absorption of UV radiation in to the skin; however, as a public health measure, sun avoidance has not been completely successful, as the common sight of beaches filled with sunbathers illustrates. Fortunately, a wealth of research aimed at additional strategies for the prevention of photoaging and skin cancer development is emerging. “Chemoprevention” refers to the prevention of photoaging and skin cancer through the use of pharmacologic agents that inhibit or reverse the process of photoaging or carcinogenesis. Carcinogenesis is a multistep process, and therefore, tumor development may be halted at several prospective points of intervention. Because skin cancer and photoaging share the same etiology, prevention of one may be helpful in the prevention of the other.

Vitamins

Although sunscreens are strongly recommended, some have questioned their effectiveness as chemopreventive agents. Compliance and efficacy could potentially increase with the availability of a once-a-day systemic sunscreen. Oxidative damage is thought to play a role in photodamage and photocarcinogenesis. As vitamin E is a potent antioxidant, it appears to be a sound contender; however, no protective effect against sunburn was demonstrated following a six-month trial of high-dose oral vitamin E.1 Similarly, a trial of high-dose systemic beta-carotene at 180 mg/day for 10 weeks resulted in only a slight increase in the minimal erythema dose (MED).2 In addition, a trial in which a combination of beta-carotene and vitamin E was given to patients was conducted.3 This combination was found to be inadequately photoprotective with an SPF of 3.

In addition to vitamin E, selenium and beta-carotene have been investigated as potential chemopreventive agents in two large, randomized, placebo-controlled trials.4,5 No effect was seen on the incidence of squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) after administration of 50 mg/day of beta-carotene for 5 years. Likewise, administration of 200 mg/day of selenium for an average of 4.5 years in 1312 patients demonstrated no effect on SCC or BCC; however, the incidence of lung, colorectal, and prostate cancers was reduced.

Beyond UV absorption, there are multiple points at which a chemopreventive agent may have clinical utility. Vitamin A and its derivatives have been proven to be effective as chemopreventive agents. Rather than functioning as sunscreens, retinoids appear to exert their effects later in the carcinogenic pathway. The chemopreventive properties of vitamin A were investigated in a large clinical trial involving 2297 patients.6 These patients had a history of more than 10 actinic keratoses and fewer than 3 skin cancers, and were considered to be at moderate risk for the development of new skin cancers. A dose of 25,000 IU of vitamin A was administered for up to 5 years. A significant reduc-
tation in SCC formation was observed, thus demonstrating the chemopreventive efficacy of vitamin A in moderate-risk patients. A follow-up study was performed in which 719 patients defined as high-risk, with a history of 4 or more skin cancers, were given 25,000 IU of oral vitamin A; however, no protective effect was observed in this high-risk group.

Vitamin A derivatives, including isotretinoin and etretinate, impart a higher safety profile, and have also been evaluated for their chemopreventive effects. Isotretinoin was initially assessed as a chemotherapeutic agent. Clinical trials with isotretinoin in the treatment of BCC demonstrated a response rate of merely 20% and a complete clearance rate of just 10%. Response rates of approximately 40% were found in trials with SCC. Isotretinoin was later studied as a chemopreventive agent. Isotretinoin significantly inhibited tumor formation during the study period in patients with xeroderma pigmentosum. The chemopreventive effect was observed two months following initiation of isotretinoin, and disappeared approximately three months after the discontinuation of isotretinoin. The rapid commencement and termination of its chemopreventive effect suggests that isotretinoin acts late in the carcinogenic pathway. Etretinate, and its replacement acitretin, have both been shown to be effective for chemoprevention in high-risk patients following organ transplantation. Vitamin A and its derivatives is the only group of chemopreventive agents that have been clearly demonstrated to be effective against cancers of the skin.

Diet

Diet has been promoted as a chemoprevention strategy; however, this is a somewhat controversial topic. While multiple reports in the medical literature and popular press suggest that diets high in fruits and vegetables result in fewer internal cancers, there appear to be an equal amount of studies that report no protective effect. Furthermore, epidemiologic studies are difficult to perform, as dietary interventions tend to be multifaceted and complex.

A connection between diet and skin cancer was first suggested in 1939 in a poorly controlled study that suggested that animals who were fed high-fat diets were more susceptible to skin cancer. More recently, studies have examined dietary lipids in experimental animals. Mice that were fed a diet with saturated fat were compared to those fed a diet with unsaturated fat. In response to UV light, fewer skin cancers developed in the group fed saturated fat. In similar studies using the South American opossum, an animal model for melanoma, a saturated fat diet resulted in fewer melanocytic tumors than unsaturated fat diets. No effect was observed on SCC development. In human studies, fewer actinic keratoses, as well as a significant reduction in new skin cancer formation, resulted during the study period in which the percentage of fat in the diet was decreased while the total amount of calories was kept constant.

It is not known whether the chemopreventive effect of such diets is a result of nutrients (carbohydrates and fat), or non-nutrients, which may be present in only trace amounts. Two promising groups of chemopreventive agents, polyphenolic antioxidants and isoflavones, have been identified in the pursuit of non-nutrients with potential chemopreventive effects that are derived from plants.

Polyphenolic antioxidants are derived from the extracts of green tea, grape seeds, and milk thistle. After water, green tea is the second most widely consumed beverage in the world. It has been widely studied for its chemopreventive effects. Epigallocatechin-3-gallate (EGCG) (a major constituent of green tea, comprising 30%–40% of its dry weight) has emerged as a promising candidate for cancer prevention studies. Despite its mixed effects on internal malignancies, green tea extracts containing EGCG and its derivatives have been observed to inhibit the growth of human melanoma cell lines in tissue culture. EGCG has also been shown to inhibit the development of UV-induced skin cancer (SCC) in mice when applied topically or administered orally. Grape seeds, which also contain polyphenolic antioxidants, have been studied as chemopreventive agents as well, and have been found to inhibit the promotion stage of two-stage chemical carcinogenesis in mouse skin. Silymarin, another polyphenolic antioxidant present in milk thistle, demonstrated significant protection against UV- and chemically-induced skin cancer formation in mice.

A second group of compounds with antioxidant activity and anticarcinogenic effects, the isoflavones, are surfacing as potential chemopreventive agents. Isoflavones are found in soybeans. Diets high in soybeans have been associated with a decreased incidence of cardiovascular disease, osteoporosis, and certain cancers. Isoflavones were determined to be the responsible constituent of the soybean, and, in particular, genistein was found to be the most potent compound. In experimental mice, when given orally or topically, genistein has inhibited chemical as well as photocarcinogenesis. Genistein’s activity is believed to be a result of the fact that it is a potent antioxidant, with the ability to downregulate signal transduction pathways related to tumor promotion. In addition, it has been observed to inhibit UVB-induced metalloproteinase expression, an enzyme implicated in photoaging. Soybean extracts are currently available in topical cosmetic products promising chemoprevention of sunburns, photoaging, and skin cancer.

Curcumin (diferuloylmethane), a substance from the
plant Curcuma longa Linn, which imparts a yellow color to curry, has been suggested to be a chemopreventive agent. Curcumin has been shown to inhibit several TPA-induced signal transduction pathways, thereby affecting stages of initiation, promotion, and progression of carcinogenesis. A recent phase I clinical trial evaluated the use of curcumin in patients with high-risk or premalignant lesions. Curcumin was found to be nontoxic at an oral dose up to 8000 mg/day when taken for 3 months, with histologic improvement seen in 2 of 6 patients with Bowen’s disease.

**Aspirin and NSAIDs**

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are another promising group of chemopreventive agents. Extensive investigation has been performed on the abilities of aspirin, indomethacin, piroxicam, and sulindac to function as successful chemopreventive agents late in the development of colon cancer. Preventive effects have also been documented in lung cancer, prostate cancer, and skin cancer.

Aspirin and NSAIDs function through modulation of the biosynthetic pathway of prostaglandins. Prostaglandins are proinflammatory and immune-regulating eicosanoids. They influence cell proliferation, tumor growth, and immune responsiveness, and are synthesized from arachidonic acid. The rate-limiting step in their production is controlled by the enzyme cyclooxygenase (COX), which exists in two isoforms, COX-1 and COX-2. COX-2 is inducible and has been implicated in the promotion stage of carcinogenesis. Aspirin and NSAIDs each inhibit both COX-1 and COX-2. Inhibition of COX-1 results in blockage of prostaglandin production in the gastric mucosa, thereby, leading to gastric bleeding. The chemopreventive activity of aspirin and NSAIDs is thought to be the result of inhibition of COX-2. Increased epidermal COX-2 expression has been observed in mouse skin that underwent chronic exposure to UVB. In the mice that demonstrated increased COX-2 expression, papillomas and SCCs eventually developed.

Medications that selectively inhibit COX-2 have been developed. Recent animal model studies have shown that celecoxib (a specific COX-2 inhibitor, developed for the treatment of arthritis) can significantly decrease skin cancer formation when administered before or during UV-light exposure. In addition, when given after UV exposure and after the first skin cancer appears, celecoxib was found to inhibit the formation of new tumors. Another study, which assessed the chemopreventive effect of celecoxib in UV-induced skin cancer in hairless mice, demonstrated that at both low doses (200 mg twice daily) and high doses (400 mg twice daily), the tumor latency period was lengthened in a dose-dependent manner. Furthermore, tumor multiplicity was decreased by approximately the same magnitude at both doses. The idea that a group of medications so extensively available may provide effective chemoprevention of cancer makes this an exceptionally exciting area of research. Several studies examining the chemopreventive activities of COX-2 inhibitors are currently underway.

Diclofenac (Solaraze) is a nonsteroidal anti-inflammatory drug that has recently been approved by the FDA for the treatment of actinic keratoses. It has properties similar to those of aspirin and ibuprofen. Diclofenac inhibits tumor-promoting substances, which are locally produced by premalignant cells. It has been found to successfully eradicate both clinically apparent AKs and lesions below the level of detection.

**Topical Agents**

Several topical agents with chemopreventive effects have been explored. Difluoromethylornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase, has been shown to decrease the formation of actinic keratoses when applied topically to human skin. Ornithine decarboxylase plays a key role in the biosynthesis of polyamines. Polyamines are necessary for cell growth and division. During tumor production, polyamine levels are increased; therefore, inhibition of polyamines may inhibit cancer. In a study in which high-risk subjects applied DFMO to one arm for six months, a significant reduction in the number of actinic keratoses was observed. Because it has been found to downregulate the expression of genes implicated in transformation into nonmelanoma skin cancer, DFMO is currently being investigated for chemoprevention of skin cancers in organ transplant recipients requiring immunosuppression, a population known to develop secondary cancers, commonly including nonmelanoma skin cancer in sun-exposed areas.

In a recent randomized study involving patients with xeroderma pigmentosum and a history of AKs or other skin cancers, topically applied T4 endonuclease V was examined as a potential chemopreventive agent. Xeroderma pigmentosum is a disease in which there is a genetic defect in DNA repair, thus leading to an increased frequency of all forms of skin cancer. T4 endonuclease V is an enzyme that functions to repair bacterial DNA. When given to humans intercellularly, it has been found to accelerate the rate of repair of sunlight-induced DNA damage. When applied topically for three months, T4 endonuclease V lowered the rate of BCC as well as of AKs, producing a 68% decrease in AKs and a 30% decrease in BCCs.

Cyclopamine (cyclopin), a substance derived from false hellebore or corn lily plants, is another agent being examined for its chemopreventive properties. Cyclo-
pamine is so named because sheep that ingested these plants gave birth to Cyclops lambs. Common BCCs and BCCs in patients with basal cell nevus syndrome result from an abnormality in genes involved in cellular signals in the growth and differentiation phases of the cell cycle. These cellular signals affect cell differentiation and are called patched and smoothed. Patched signals promote differentiation, while smoothed signals promote cell growth without differentiation. If the balance between patched and smoothed signals is upset, carcinogenesis and unregulated cell growth may result. Multiple basal cell carcinomas develop in the absence of patched, while severe birth defects are the result of deficiencies in smoothed. In basal cell nevus syndrome, approximately one half of patched genes are missing. Sunlight or x-ray exposure, in addition to deficient patched genes, may cause vulnerable cells to become malignant. Solitary BCCs may develop in those without basal cell nevus syndrome, subsequent to chronic sun or other UV exposure, which may in time debilitate patched genes. Cyclopamine has been found to be a potent stimulator of the patched gene.31 It has been demonstrated to reverse the carcinogenic effects of excess smoothed or deficient patched, and following further research, may one day prove to be an effective chemopreventive agent.

Conclusions

Further studies are warranted to identify and determine the safety and efficacy of new chemopreventive agents. As multiple targets in the carcinogenic pathway may be utilized in the development of chemoprevention, we can expect a greater number of effective agents to emerge. Both systemic and topical agents may soon be available that effectively prevent photoaging and skin cancer development.

References

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