Melanoma chemoprevention

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Background: Despite efforts to promote sun protection behaviors, melanoma incidence continues to increase. The prognosis of advanced melanoma remains extremely poor in spite of treatment advances, emphasizing the importance of exploring additional preventive measures.

Objective: We sought to summarize the results of published research on candidate chemoprevention agents for melanoma.

Methods: We conducted a narrative review of the literature.

Results: Investigation into a possible role in melanoma chemoprevention continues for multiple agents, including sunscreen, lipid-lowering medications, nonsteroidal anti-inflammatory drugs, dietary nutrients, immunomodulators, and other drugs, including retinoids, difluoromethylornithine, and T4 endonuclease V.

Limitations: Systematic review of the literature was not performed.

Conclusion: Because no agent yet emerges as a clear choice for effective melanoma chemoprevention, sun avoidance and sun protection remain the mainstay of melanoma prevention for persons at high risk. (J Am Acad Dermatol 2006;55:849-61.)

Melanoma, a malignant neoplasm of melanocytes, is the most deadly form of skin cancer. The incidence of melanoma continues to increase despite public health initiatives that have promoted sun protection. In the United States, 59,580 newly diagnosed invasive melanomas and 7700 deaths were anticipated in 2005, making melanoma the fifth most common invasive cancer in men and sixth most common in women.[1] Those at risk for melanoma include persons with fair skin, numerous common nevi or large congenital nevi over greater than 5% of body surface area, or a personal or family history of the disease.[1-3] UV light exposure plays a complex role in melanoma development. Childhood sunburns and intermittent sun exposure correlate positively with melanoma risk.[4,5] Although up to 83% of melanomas are diagnosed while confined to the local site,[1] the lack of effective treatment leaves those given a diagnosis of advanced melanoma with a dismal prognosis. The 5-year relative survival for patients who originally present with melanoma confined to the local site is 98%, but those with regional and distant metastases have a 5-year survival of only 60% and 16%, respectively.[1]

The increasing incidence of melanoma and its poor prognosis in advanced stages mandate the investigation of novel approaches of prevention such as chemoprevention. Chemoprevention has been used to reduce the incidence of other cancers. Substances currently used to prevent malignancy in specific groups of patients at high risk include

Abbreviations used:

COX:	cyclo-oxygenase
DFMO:	difluoromethylornithine
EGCG:	epigallocetechin 3-gallate
NSAID:	nonsteroidal anti-inflammatory drug

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tamoxifen and aromatase inhibitors for breast cancer,[6] finasteride for prostate cancer,[7] and nonsteroidal anti-inflammatory drugs (NSAIDs) for colon cancer.[8] The use of topical diclofenac to prevent actinic keratoses from progressing to invasive squamous cell carcinoma provides an example of chemoprevention currently used in dermatology.[9] Melanoma chemoprevention would use agents that prevent the development of melanoma.[10]

There are 3 different forms of melanoma chemoprevention. Primary chemoprevention would prevent occurrence of melanoma in healthy individuals. Secondary chemoprevention aims to prevent premalignant melanoma precursors from becoming melanoma. Finally, tertiary chemoprevention seeks to prevent melanoma in patients with treated melanoma and no current signs of disease.[11] Ideally, medications would be inexpensive, easily administered, and have minimal side effects. Such agents would be especially valuable for patients at high risk. In evaluating effectiveness, chemoprevention interventions would best be measured by ability to reduce melanoma incidence and melanoma mortality.

Enhanced understanding of melanocyte biology, intriguing laboratory results, and unexpected observations from cardiovascular disease trials have fueled speculation that melanoma chemoprevention may be possible.[12] To date, a variety of agents, exerting effects through different mechanisms, have been studied through in vitro, animal, and human models with varying results. This review will summarize recent evidence regarding the ability of those agents to inhibit the development of melanoma. The agents are listed in Table I, along with their side effects, whereas Table II summarizes their potential mechanisms of action.

SUNSCREENS

Although some studies have found a decreased melanoma risk among sunscreen users,[13-16] others have demonstrated no association[17-19] or even increased melanoma risk associated with sunscreen use.[20-22] Methodologic difficulties may explain this discrepancy. Factors related to sun exposure such as frequency, intensity, and temporal association with melanoma diagnosis, and variables associated with sunscreen use such as correct usage, consistency of use, and sun protection factor are difficult to assess based on retrospective recall, are difficult to accurately quantify, and have often not been adequately captured.[23-25] In addition, many studies have not controlled for sun sensitivity.[19]

In addition to concerns regarding the validity of the findings, several theories have been postulated to explain why sunscreens might not be protective. First, the spectrum of UV radiation causing erythema may differ from the spectrum promoting melanoma. Sunscreens have traditionally been designed to prevent erythema by blocking UVB, leaving users relatively unprotected from wavelengths such as UVA, which may also promote melanoma development.[25-27] Sunscreen use, especially with a higher sun protection factor, may lead to increased duration of sun exposure, including portions of the UV spectrum that may contribute to melanoma development but that are not affected by traditional sunscreens.[21,22,24] Currently available sunscreens often have both UVA and UVB protection, but studies distinguishing between use of UVA/UVB sunscreens and UVB-only sunscreens have not yet been performed.

Another theory suggests that irregular use of sunscreens increases intermittent UV exposure. Although regular sunscreen application prevents thymine dimer formation in DNA, irregular sunscreen application may not.[28] A third hypothesis suggests that vitamin D synthesized in response to UV exposure may counter cancer.

Despite the controversy, photoprotection, including both sun avoidance and broad-spectrum UVA/UVB sunscreen use, remains an important part of melanoma prevention. Used properly, sunscreens block mutagenic UV rays and prevent sunburn, factors shown to have an association with melanoma.[4,5] Moreover, recent epidemiologic and small randomized trials with short follow-up time have shown that sunscreen use reduces the development of melanocytic nevi, a known risk factor for melanoma.[29-32] Finally, extensive evaluation and market history have shown sunscreen use to have minimal harm, an important factor in a preventative agent.[33]

ANTILIPIDEMICS

Because cancerous cells and normal cells metabolize cholesterol differently,[34] altering cholesterol metabolism may prevent carcinogenesis or selectively inhibit tumor growth.[35,36] 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have been proposed to decrease incidence of melanoma and increase effectiveness of treatment. In vitro and animal studies show a potentially therapeutic role for melanoma and other cancers through pleiotropic anti-inflammatory, immunomodulatory, and antiangiogenesis mechanisms.[37] More specifically, statins have been shown to: (1) inhibit proliferation and invasion through inhibition of isoprenoid protein modification required by signaling proteins such as Ras, Rac, and Rho in vitro[38]; (2) induce melanoma cell apoptosis through a geranylation-specific mechanism[39]; (3) inhibit