The Challenge of Melanoma Chemoprevention

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ABSTRACT

Melanoma is a treatment-resistant cancer of melanocytes. There is a serious unmet need for chemopreventive agents that can inhibit their evolution from preexisting dysplastic nevi. Low-dose aspirin and NSAIDs are potential chemopreventive candidates because they inhibit the enzyme COX-2 which has a number of procarcinogenic effects. Unfortunately, the clinical trial reported by Okwundu and colleagues in this issue of *Cancer Prevention Research* did not show an effect of aspirin on biomarkers associated with progression of premalignant dysplastic nevi to melanomas. Further clinical trials with other aspirin or NSAID biomarkers or clinical trials with other potential chemopreventive agents offer hope to those who are at increased risk for melanomas.

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Melanoma is an aggressive, treatment-resistant cancer of melanocytes. In the United States alone, more than 101,000 new invasive melanomas and 7,180 deaths are estimated to occur in 2021. In most other malignancies, the incidence has either stabilized or declined; in melanoma, they continue to rise. Melanomas often begin as benign nevi, some of which progress over long periods of time to become invasive and metastatic melanomas. The risk factors for melanoma are well defined and include exposure to UV radiation, (intermittent high intensity sun exposure, use of tanning beds, and psoralen photochemotherapy); physical characteristics many of which are associated with polymorphisms in the melanocortin-1 receptor (*MC1R*; i.e., fair skin and freckling, blue eyes, red hair, and inability to tan), individuals with large numbers of melanocytic nevi, and those who have previously been diagnosed with a melanoma. There are families who are prone to multiple melanomas and in these individuals the melanomas often begin at a young age. Individuals from these families usually have more than 50 nevi, many of which have atypical clinical and pathologic features. Up to 40% have germline mutations in the *CDKN2A* gene. Thus, there is a large population of individuals for whom chemopreventive agents would be valuable. Because of this and the clinical importance of the problem, there has been great interest in identifying methods for deterring or delaying premalignant nevi from evolving into melanomas (1).

A barrier to melanoma chemoprevention is the difficulty in identifying appropriate calibrated endpoints to evaluate the efficacy of test agents. It is difficult to determine which pigmented lesions will ultimately progress from dysplastic nevi into melanomas based on clinical appearance. Screening for potential chemopreventive agents relies on predictive biomarkers and reliable animal models that mimic the progression of melanoma from melanocytic nevi. Unfortunately, there are few generally accepted biomarkers and only a small number of animal models to use. Changes in histopathologic features of dysplastic nevi have proven to be unreliable as biomarkers because of variability in interpretation among dermatopathologists.

Increases in STAT3 expression and confocal microscopy have been proposed as potential biomarkers (1). There are several mouse melanoma models, but they are largely restricted to transplantable syngeneic melanoma lines or transgenic mice with enforced expression of mutant oncogenes (*N-ras*, *p16/INK4a*, *HGF*, *BRAF*, *PTEN KO*, etc.). While they are important for assessing potential treatments and conducting mechanistic studies, genetically engineered models rapidly develop melanomas without prior evidence of having been dysplastic nevi, making it difficult for prevention studies of preneoplastic nevi that progress to invasive melanomas. In a mouse model we have developed, topically applied dimethylbenz(a)anthracene, a polyaromatic hydrocarbon, followed by repeated exposure to 12-O-tetradecanoylphorbol 13-acetate (TPA) or UVA radiation, results in spontaneous nevus formation. Approximately half progress to melanomas whereas the other half regress (2). The melanomas accurately recapitulate many of the molecular changes found in humans and may therefore be a potential animal model to use.

Because UV radiation exposure is a contributing factor for most melanomas, sunscreens are strongly recommended for people at risk. Clinical information supports their efficacy. In a study in which people in Australia were treated with a Sun Protection Factor (SPF) 15 sunscreen for5 years and compared with individuals who only used them sporadically, there was a

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50% reduction in melanoma incidence in the regular sunscreen group (3). This was statistically significant for invasive melanomas, but not for melanomas *in situ*. Also, in a prospective population-based study of Norwegian women ages 40 to 75 years and followed for a mean of 10.7 years, those who applied high SPF (≥15) sunscreens had an 18% reduction in melanoma incidence compared with those who used low SPF (<15) sunscreens (4). Despite the benefits of sunscreens, there is inconsistent patient compliance with their use, large amounts of sunscreen are required to achieve the full SPF value on a product label, and there is no effect of sunscreens on prior UV damage. Notwithstanding, the incidence of melanoma has continued to rise over the past several decades even with their use.

Several agents have been examined for melanoma prevention with negative results or potential safety issues (1). These include statin lipid lowering agents that inhibit farnesylation of proteins in the ras signal transduction pathway; selenium, metabolites of which render melanoma cells more susceptible to apoptosis and proliferation inhibition *in vitro*; and N-acetylcysteine, which has antioxidant effects.

Aspirin and NSAIDs have been attractive candidates for melanoma chemoprevention. They have already been shown to have chemopreventive activities in keratinocyte carcinomas (KC) and other malignancies (5, 6). Aspirin and NSAIDs inhibit the enzyme COX-2 which is necessary to produce prostaglandin E2 (PGE2). PGE2 has several procarcinogenic activities. It is proinflammatory, stimulates cellular proliferation and angiogenesis, promotes epithelial–mesenchymal transition, and regulates antitumor immunity. Aspirin is particularly appealing because is cardioprotective and is not associated with increased major adverse cardiovascular events. The Grossman laboratory has carefully investigated aspirin as a potential melanoma chemopreventive agent (7–9). Using melanoma cell lines, aspirin significantly reduced colony formation and cell motility and diminished UV-induced DNA damage, both cyclobutane pyrimidine dimers and 8-hydroxydeoxyguanosine. *In vivo* studies employed TpN^{61R} transgenic mice have melanocyte-specific somatic gene mutations in *NRas* and *Cdkn2a* ($p16^{INK4a}$). These mice develop melanomas after a single neonatal exposure to UV radiation. Treatment with aspirin *in utero* and after birth inhibited UVB-induced PGE2 concentrations in skin and plasma. Although aspirin did not reduce the number of tumors or increase their latency, it did inhibit tumor growth rates and DNA damage. These antagonistic effects of aspirin on parameters associated with melanomagenesis were the impetus to a clinical trial examining the chemopreventive activity of aspirin in melanocytic nevi.

In the report in this issue of *Cancer Prevention Research*, Okwundu and colleagues conducted a randomized placebo controlled clinical trial examining aspirin on biomarkers associated with progression of dysplastic nevi to melanoma (8). Ninety-five subjects were randomized to receive 81-mg aspirin, 325-mg aspirin, or placebo for 1 month. One nevus was exposed to solar simulated radiation. One day later the nevus was removed and examined for markers of inflammation and DNA damage. There were no significant differences in T-cell or macrophage populations or in numbers of nevus cells with cyclobutane pyrimidine dimers and 8- hydroxydeoxyguanosine. While this was a setback for melanoma prevention, a different protocol or examination of other biomarkers might offer a pathway for further investigation of aspirin and NSAIDs.

Table 1. Potential agents for melanoma chemoprevention.

Agent	Mechanism of action
T4 Endonuclease V	DNA damage repair
MC1R agonists	Increase pigmentation
SIK inhibitors	Increase pigmentation
Nicotinamide	DNA damage repair
Aspirin	Inhibit DNA damage, PGE2 inhibition
NSAIDs	PGE2 inhibition
Retinoids	Proliferation inhibitors
Vitamin D analogues	Antioxidant activities, DNA damage repair, inhibit angiogenesis, inhibits inflammation
Phytochemicals (Polypodium leukotomos, EGCG, Sulphoraphane, Grape proanthocyanidins, Fisetin)	Increase pigmentation, anti oxidants, DNA damage repair, reverse photoimmunosuppression

Other potential chemopreventive agents for melanoma are being investigated (**Table 1**; ref. 1). Nicotinamide, a member of the B3 group of vitamins, is a potentially interesting compound. This agent augments DNA damage repair and in phase III clinical trials, it protects high-risk individuals against basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Experimental data suggest that it may be useful for melanoma chemoprevention as well (10).

Melanocytes express MC1R, which activates a pathway that stimulates eumelanin synthesis. Pharmacologic MC1R agonists have received regulatory approval in some countries for photoprotection in erythropoietic protoporphyria. By increasing pigmentation in skin, MC1R agonists may retard progression of dysplastic nevi to melanoma. Another approach to augmenting pigmentation is administration of Salt Inducible Kinase (SIK) inhibitors, which increase melanin production in animal models. Clinical trials have not yet been initiated and there is a theoretical concern that activating this pathway in dysplastic nevi or melanomas could increase their progression or growth.

Vitamin D3 has potent antimelanoma activities, and defects in vitamin D signaling contribute to melanomagenesis (11). Vitamin D3 hydroxyderivatives attenuate tumor initiation and promotion by its antioxidant activities, its ability to stimulate DNA damage repair, retard angiogenesis, and restrain inflammation. Low serum 25-hydroxyvitamin D3 levels are associated with thicker tumors and poorer prognosis. Decreases in vitamin D receptor and CYP27B1

(an enzyme activating 25-hydroxyvitamin D3) expression are associated with increased aggressiveness of melanocytic lesions. Studies examining vitamin D levels and intake on melanoma have been unrewarding and larger doses of vitamin D have the side effect of hypercalcemia. Noncalcemic analogues of vitamin D also have activities that protect against melanoma and may have potential for melanoma chemoprevention.

There is an inverse relationship between vitamin A consumption and melanoma risk in large case–control studies, although the data on vitamin A and its precursor β-carotene in clinical trials have been conflicting (1). In one clinical trial, clinical and histologic improvement in dysplastic nevi was observed following topical application of all *trans*-retinoic acid. Although no improvement was observed with oral isotretinoin, other topical and systemic retinoids are being synthesize which may have potential.

Phytochemicals are being investigated as possible chemopreventive agents for melanoma and nonmelanoma skin cancer. Depending on the specific phytochemical, their actions include an antioxidant effect, promotion of DNA damage repair, and inhibition of photoimmunosuppression. Randomized clinical trials have not yet been conducted with these agents for melanoma.

Identification of agents that prevent the progression of dysplastic nevi to melanoma has been challenging. Further studies with aspirin examining other biomarkers and clinical trials with the pipeline of other potential agents may ultimately meet the hopes and expectations of individuals at risk for melanoma for a medication that will prevent this serious disease.

Authors' Disclosures

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