From the Cochrane Library: Statins and Fibrates for Preventing Melanoma

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Dear Editor,

Melanoma has a lower incidence than non-melanoma skin cancers; however, it represents 41% of skin-related deaths in the United States [1]. Pharmaceutical prophylaxis for melanoma is lacking; prevention relies on skin cancer screening and education to reduce risk. A 2005 Cochrane review, “Statins and fibrates for preventing melanoma,” provides analysis of the available data regarding the effectiveness of these lipid-lowering medications in melanoma prevention [2].

This review [2] assessed data from 16 randomized controlled trials of statin or fibrate versus control, to examine their role in melanoma prevention. Among the qualifying trials, 3 statins (lovastatin, pravastatin, simvastatin) and 3 fibrates (bezafibrate, clofibrate, gemfibrozil) were used. A total of 66 melanomas were identified in the treatment group versus 86 in the control group. For statin trials, this translated to an odds ratio (OR) of 0.90 (95% confidence interval [CI] 0.56–1.44) and for fibrates, OR 0.58 (95% CI 0.19–1.82). Only two studies reached statistical significance, demonstrating decreased

melanoma diagnoses among those taking lipid-lowering agents: lovastatin (OR 0.52, 95% CI 0.27–0.99) and gemfibrozil (OR 0.11, 95% CI 0.01–0.87). All other subgroup analyses (by gender, after 2 years of participation, by funding) failed to show significant differences between treatment and control.

Previous studies suggest a reduced risk of melanoma for those taking antihyperlipidemics, and in animal models, statins induced apoptosis and slowed tumor growth. However, it is unclear whether these findings are generalizable and can reliably translate to real-world populations. Data assessed in this review are not sufficient to refute or support the utility of statins or fibrates in preventing melanoma, suggesting a 10% and 42% reduction in melanoma diagnoses for statins and fibrates, respectively, though failing to reach statistical significance.

The benefit of antihyperlipidemics for melanoma prevention may be specific to subsets of the population based on characteristics (e.g., female sex, comorbid heart disease, or dyslipidemia) and risk factors (family history, dysplastic nevi, increased age, white race). Clinicians should weigh the harms versus benefits of lipid-lowering drugs, considering potential side effects: a meta-analysis reported an increase in death rates not related to heart disease [2] and an association between longer duration of statin use and higher basal cell carcinoma risk in men ($p_{\text{trend}} = 0.003$) [3].

Statins and fibrates may play a larger role in tertiary prevention for melanoma. Altered lipid metabolism in melanoma contributes to its aggressiveness and plasticity [4]. Further, a 2020 *Cancers* review affirmed their ability to decrease melanoma progression through multiple mechanisms, as well as an association of statin use with reduced recurrence of ulcerated primary melanoma and reduced Breslow thickness [4]. Notably, Pellerin et al.'s review evaluates other mediators of lipid metabolism in addition to those impacting cholesterol synthesis: SphK1, SCD1, COX-2, and others. These components of the lipid metabolic network, not considered by this review, may be pivotal to unlocking pharmacologic melanoma prevention.

The significant burden of melanoma merits continued discussion of lipid-altering medications as potential chemopreventive agents for high-risk patients, and as therapeutic agents for aggressive disease. As novel treatment strategies involving lipid metabolism emerge, so too does the potential for melanoma prevention.

Key Message

Statins and fibrates for melanoma prevention remain controversial; however, other lipid metabolism mediators need investigation.

References

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Conflict of Interest Statement

Dr. Dellavalle is a Joint Coordinating Editor for *Cochrane Skin*, a dermatology section editor for *UpToDate*, a Social Media Editor for the *Journal of the American Academy of Dermatology (JAAD)*, a Podcast Editor for the *Journal of Investigative Dermatology (JID)*, and Editor in Chief of *Journal of Medical Internet Research (JMIR Dermatology)*. He is a coordinating editor representative on *Cochrane Council*. Dr. Sivesind serves as a Section Editor for *JMIR Dermatology*.

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Abigail L. Meckley is the lead author in authoring text, study design, and literature review. Michelle Militello, Torunn E. Sivesind, Lisa Schilling, and Robert P. Dellavalle contributed as co-authors in research question development and manuscript editing.