Meta-Analysis of the Association Between Phosphodiesterase Inhibitors (PDE5Is) and Risk of Melanoma

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Abstract

The US Food and Drug Administration recently announced the need to evaluate the association between PDE5Is and melanoma. We performed a meta-analysis on the association between PDE5i and melanoma using random effects models and examined whether it met Hill’s criteria for causality. A systematic search of Medline, EMBASE, and the Cochrane Library from 1998 to 2016 identified three case-control studies and two cohort studies, including a total of 866,049 men, of whom 41,874 were diagnosed with melanoma. We found a summary estimate indicating an increased risk of melanoma in PDE5i users (relative risk = 1.11, 95% confidence interval = 1.02 to 1.22). However, the association was only statistically significant among men with low PDE5i exposure (not high exposure) and with low-stage melanoma (not high stage), indicating a lack of dose response and biological gradient. PDE5i use was also associated with basal cell cancer, suggesting a lack of specificity and likely confounding by ultraviolet exposure. Thus, although this meta-analysis found a statistically significant association between PDE5i and melanoma, it did not satisfy Hill’s criteria for causality.

Phosphodiesterase inhibitors (PDE5i) are first-line drugs for erectile dysfunction, which is estimated to affect 20% of men age 60 years and older and 30% of men age 70 years and older (1). Phosphodiesterase type 5 is downregulated in BRAF mutations commonly seen in melanoma (2), raising the question of whether pharmacologic inhibition could increase melanoma risk.

In 2014, Li et al. found an association between sildenafil use and melanoma risk (3). Since then, additional studies have been published using large US and European databases (4–6). In 2016, the US Food and Drug Administration placed PDE5i on the watch list of drugs with possible safety issues (7). Our objective was to perform a meta-analysis of published data on the association between PDE5i and melanoma risk. In particular, we sought to determine whether there is an association that meets Hill’s causal criteria including strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy (8).

A systematic search was performed using Medline, EMBASE, and the Cochrane Library for publications from 1998 (when PDEI were introduced) to August 2016. The search string was (PDE5 OR phosphodiesterase type 5 OR sildenafil OR tadalafil OR avanafil) AND melanoma (Supplementary Figure 1, available online). From 62 nonduplicate citations screened, four were included in the quantitative synthesis with a moderate to serious risk of bias (Supplementary Table 1, available online) (9).

Data were extracted using a standardized template, including quantitative estimates of the association between PDE5i and melanoma, also stratified by the extent of exposure and melanoma stage. We also examined the association between PDE5i and basal cell carcinoma.
Sildenafil use was statistically significantly associated with risk (RR = 1.15, 95% CI = 1.09 to 1.21) and a statistically significantly greater risk of melanoma, basal cell cancer, and solar keratosis, whereas there was no statistically significant association between PDE5i and colorectal cancer, a malignancy not linked to UV exposure. Men with solar keratosis, a proxy for sun exposure, were more likely to use PDE5i subsequently, providing further evidence of sun exposure as a confounder.

Finally, Pottegard et al. performed separate case-control analyses using large registries from Denmark and California (11). In both, they found no statistically significant association between
PDE5i ever use or high use and overall melanoma risk. There was also no statistically significant association between PDE5i use and aggressive melanoma. Notably, both PDE5i use and skin cancer are strongly associated with socioeconomic status, suggesting potential for confounding by lifestyle factors. The increased risk of in situ melanoma among PDE5i users and reduction in advanced disease also raises the possibility of detection bias.

Given that PDE5i were placed on the Food and Drug Administration watch list and the recent publication of several large studies, we performed the first meta-analysis on PDE5i and melanoma. Strengths of our study include the large sample size, incorporating data sources from multiple countries. A limitation is that the meta-analysis is based on few estimates and not all included studies provided data on dose response, stage, or other skin cancers, reducing the number of available participants for subset analyses. There is also potential for bias and misclassification of outcome in the primary studies, given the challenges of accurately diagnosing melanoma (particularly in situ melanoma) (12).

In conclusion, a meta-analysis of published studies showed a weak association between PDE5i and melanoma that did not meet Hill’s causal criteria. The lack of dose response, biological gradient, and specificity suggest against a causal relationship. The observed association may be due to confounding from other factors, in particular, sunlight exposure.

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