

BRIEF COMMUNICATION

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 firstline 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 PDE5 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.

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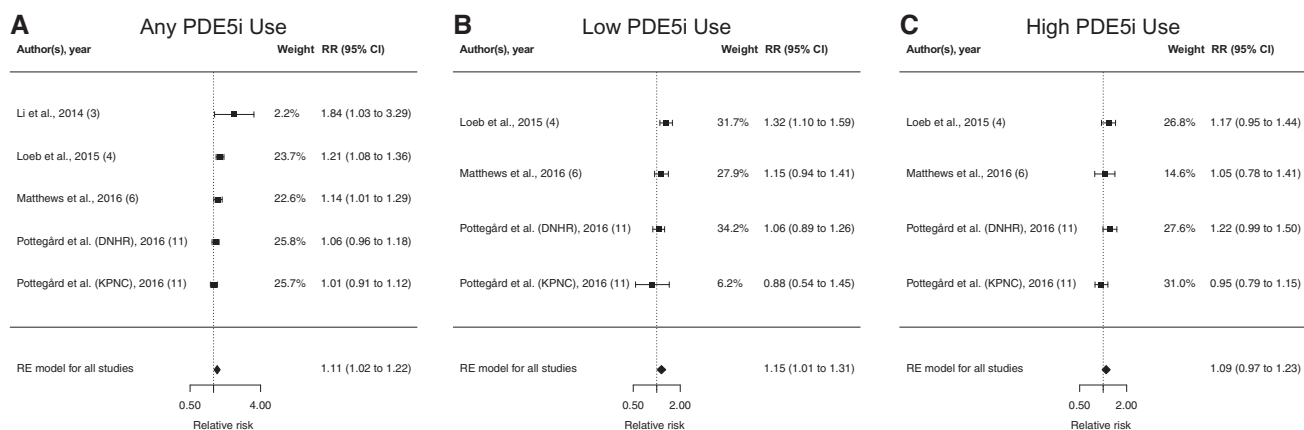


Figure 1. Association between any, low, and high use of phosphodiesterase inhibitors (PDE5i) and risk of melanoma. **A)** Any PDE5i exposure. **B)** Low PDE5i exposure. **C)** High PDE5i exposure. Low PDE5i exposure was defined in each study as follows: Loeb et al.: one prescription; Matthews et al.: one prescription; Pottegård Danish Nationwide Health Registries (DNHR): fewer than 20 tablets; and Pottegård Kaiser Permanente Northern California (KPNC): fewer than 20 tablets. High PDE5i exposure was defined in the studies as follows: Loeb et al.: six or more prescriptions, Pottegård DNHR: 100 or more tablets; and Pottegård et al. KPNC: 100 or more tablets. The center of each black square is placed at the point estimate; each horizontal line shows the 95% confidence interval (CI) for the estimate for each study. The diamond represents the summary estimate. Statistical weight estimated as for random effect models, accounting for both within-study variance and between-study variance. Test for heterogeneity: **A)** $P = .06$, $I^2 = 55.9\%$, $T^2 = 0.0053$. **B)** $P = .25$, $I^2 = 27.0\%$, $T^2 = 0.0046$. **C)** $P = .30$, $I^2 = 18.7\%$, $T^2 = 0.0029$. All statistical tests were two-sided. Summary risk estimate after exclusion of each respective study: excluding Li et al.: relative risk (RR) = 1.10, 95% CI = 1.02 to 1.19; excluding Loeb: RR = 1.08, 95% CI = 0.98 to 1.19; excluding Matthews: RR = 1.11, 95% CI = 0.99 to 1.25; excluding Pottegård (DNHR): RR = 1.06, 95% CI = 0.96 to 1.18; excluding Pottegård (KPNC): RR = 1.15, 95% CI = 1.04 to 1.26. CI = confidence interval; DNHR = Danish Nationwide Health Registries; KPNC = Kaiser Permanente Northern California; RR = relative risk.

Random effects models were used to calculate summary statistics given the different designs of the included studies. If multiple risk estimates were reported, the multivariable-adjusted estimate was used. Heterogeneity was estimated by use of the chi-square statistic and quantified by use of the I^2 values (<http://handbook.cochrane.org>). All statistical tests were two-sided, and a P value of less than .05 was considered statistically significant.

Three case-control studies and two independent cohort studies were identified including 866 049 men, of whom 41 874 were diagnosed with melanoma. PDE5i users had an increased risk of melanoma (relative risk [RR] = 1.11, 95% confidence interval [CI] = 1.02 to 1.22) (Figure 1). The heterogeneity between studies did not reach statistical significance ($I^2 = 55.9\%$, $P = .06$).

Only low PDE5i exposure was associated with increased risk (RR = 1.15, 95% CI = 1.01 to 1.31), whereas high exposure was not (RR = 1.09, 95% CI = 0.97 to 1.23) (Figure 1). The increase in risk of basal cell carcinoma (RR = 1.16, 95% CI = 1.13 to 1.20) was similar to the increased risk of melanoma (Supplementary Figure 2, available online). Finally, two publications reported stage-specific estimates in three different populations (Figure 2). High PDE5i exposure was associated with an increased risk of stage 0 melanoma (RR = 1.45, 95% CI = 1.09 to 1.92), but decreased risk of stage II to IV melanoma (RR = 0.67, 95% CI = 0.46 to 0.97). Our meta-analysis of four observational studies on PDE5i and melanoma found a statistically significant association. However, it did not meet five of Hill's nine causal criteria, suggesting against a causal relationship.

The first study on this topic examined 25 848 US health professionals, of which 6% self-reported ever using sildenafil (3). Sildenafil use was statistically significantly associated with melanoma (adjusted hazard ratio [HR] = 1.84, 95% CI = 1.04 to 3.22) but not with other skin cancers. No stage-specific results

were reported, sildenafil use was only assessed once, and there were only 14 cases of melanoma among sildenafil users.

The next study used nationwide Swedish registries in Prostate Cancer data Base Sweden (PCBaSe), comparing 4065 melanoma cases with 20 325 age-matched controls (4,10). Overall, 435 cases and 1713 controls were exposed to PDE5i, based on data from the Prescribed Drug Register documenting all prescriptions since July 2005. Although there was an increased overall risk of melanoma among PDE5i users, there was no dose-response relationship, nor an increased risk of high-stage disease. PDE5i users were also statistically significantly more likely to be diagnosed with basal cell skin cancer, indicating a lack of specificity.

Two subsequent studies both used data from the UK Clinical Practice Datalink. Among men with erectile dysfunction, Lian et al. found no statistically significant relationship between PDE5i use with melanoma (328 events/491 478 person-years among PDE5i users vs 112/207 001 person-years in nonusers, adjusted HR = 1.18, 95% CI = 0.95 to 1.47), nor with other skin cancers (5). However, subset analysis found a statistically significantly increased risk of melanoma in men with seven or more PDE5i prescriptions (or ≥ 25 pills) and a statistically significantly increased risk of basal cell cancer with two to five PDE5i prescriptions. Another study by Matthews et al. used the same registry but selected participants based on PDE5i prescriptions (6). Compared with matched controls, PDE5i users had 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, Pottegård et al. performed separate case-control analyses using large registries from Denmark and California (11). In both, they found no statistically significant association between

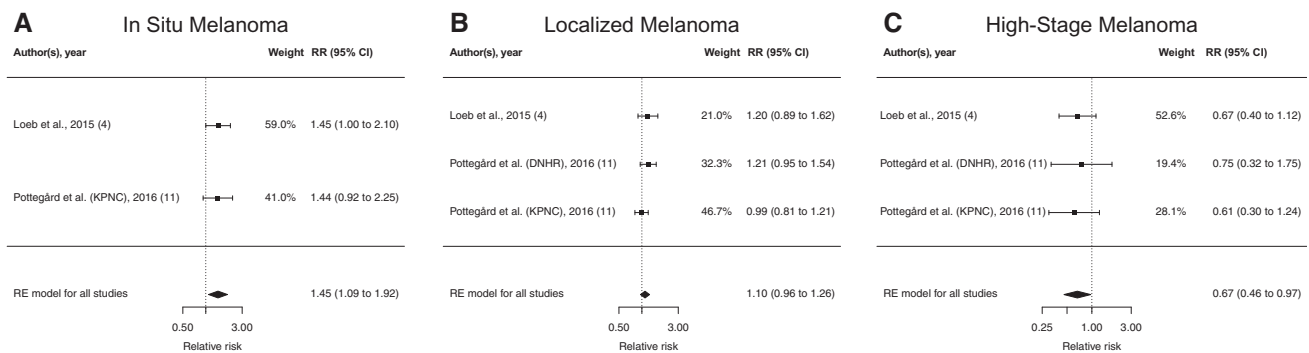


Figure 2. Association between high use of phosphodiesterase inhibitors (PDE5i) and risk of melanoma according to stage. **A)** In situ melanoma. **B)** Localized melanoma. **C)** High-stage melanoma. High PDE5i exposure was defined in the studies as follows: Loeb et al.: six or more prescriptions; Pottegard et al. Danish Nationwide Health Registries (DNHR): 100 or more tablets and Kaiser Permanente Northern California (KPNC): 100 or more tablets. The center of each black square is placed at the point estimate; each horizontal line shows the 95% confidence interval (CI) for the estimate for each study. The diamond represents the summary estimate. Statistical weight estimated as for random effect models, accounting for both within-study variance and between-study variance. Test for heterogeneity: **A)** $P = .98$, $I^2 = 0.0\%$, $T^2 = 0$. **B)** $P = .37$, $I^2 = 0.0\%$, $T^2 = 0$. **C)** $P = .93$, $I^2 = 0.0\%$, $T^2 = 0$. All statistical tests were two-sided. CI = confidence interval; DNHR = Danish Nationwide Health Registries; KPNC = Kaiser Permanente Northern California; RR = relative risk.

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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