
Phosphodiesterase type 5 inhibitors and risk of melanoma: a meta-analysis

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CAPSULE SUMMARY

- Previous studies reported conflicting results on possible associations between use of phosphodiesterase type 5 (PDE5) inhibitors and the risk of melanoma.
- This meta-analysis of five observational studies suggested a slight but significant association between PDE5 inhibitors and both melanoma and basal cell carcinoma with some evidence of heterogeneity.
- There were several limitations of this study, and future well-conducted prospective studies are warranted to assess this modest association.

ABSTRACT

Background: The association between phosphodiesterase type 5 (PDE5) inhibitors and melanoma risk is controversial.

Objective: We quantify the association between use of PDE5 inhibitors and melanoma.

Methods: We systematically searched PubMed, Embase, CENTRAL, Web of Science, and ClinicalTrials.gov for studies up to July 13, 2016 evaluating the association between PDE5 inhibitors and skin cancer. Random effects meta-analyses were used to calculate the adjusted odds ratio (OR) with 95% confidence interval (CI).

Results: Five observational studies were included. Compared with PDE5 inhibitor non-use, PDE5 inhibitor use was slightly but significantly associated with increased risk of melanoma (OR 1.12, 95% CI 1.03-1.21) and basal cell carcinoma (BCC) (OR 1.14, 95% CI 1.09-1.19), but not squamous cell carcinoma (SCC). For melanoma risk, none of the pre-specified factors (dose of PDE5 inhibitors, study design, and study region) significantly affected the results ($P > 0.05$). Our sensitivity analysis confirmed the stability of the results.

Limitations: We included only observational studies, which had some heterogeneities and inconsistent controlling for potential confounders.

Conclusions: Use of PDE5 inhibitors may be associated with a slightly increased risk of melanoma and BCC, but not SCC. However, further large well-conducted prospective studies with adequate adjustment for potential confounders are required for confirmation.

Key works: PDE5 inhibitor; melanoma; basal cell carcinoma; squamous cell carcinoma;
meta-analysis

Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil, and vardenafil inhibit cyclic guanosine-3', 5'-monophosphate (cGMP)-degrading PDE5A in the vascular smooth muscle and are widely used to treat erectile dysfunction¹. Interestingly, activation of this cGMP pathway has been shown to promote melanoma cell growth and migration^{2, 3}, and this link has recently been confirmed⁴. These laboratory observations have prompted several observational studies assessing the association between PDE5 inhibitors and risk of melanoma⁵⁻⁹.

In 2014, the first cohort study on this subject (Li *et al.*) among a US-based cohort of male health professionals indicated that self-reported use of PDE5 inhibitors was significantly associated with higher risk of melanoma compared to non-use⁵. However, their results were based on only 142 melanoma cases, of whom 14 used sildenafil. Since Li *et al.*, four additional studies have been published. A nested case-control study (Loeb *et al.* 2015) suggested a modest association between PDE5 inhibitors and risk of melanoma but did not meet several of Hill's causality criteria⁶. However, two epidemiological studies indicated no association^{7, 9}. Given these inconsistencies among individual studies, it is not possible to determine whether there is a link between PDE5 inhibitors and risk of melanoma.

PDE5 inhibitors are an effective intervention and are recommended as first-line treatment for erectile dysfunction, which affects over 18 million men in the US, or up to 20% of males aged 20 years or older¹⁰. With the expiration of the patents on sildenafil and other PDE5-inhibitor drugs, lower costs and more direct-to-consumer advertising will certainly increase the number of users. Understanding the possible connections

between PDE5 inhibitors and the incidence of melanoma is an important public health issue.

We therefore conducted a study-level meta-analysis of available evidence from observational studies to quantify the possible association between use of PDE5 inhibitors and risk of skin cancers. No randomized trials were available on this association. We also performed a cumulative meta-analysis and sensitivity analysis to assess the robustness of the results from available studies.

Methods

Search strategy and study selection

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and ClinicalTrials.gov to identify randomized trials or observational studies published up to July 13, 2016 that evaluated the association between exposure to PDE5 inhibitors and risk of skin cancer. We searched on combined terms-“(sildenafil or vardenafil or avanafil or tadalafil or phosphodiesterase type 5 or phosphodiesterase-5 or PDE5) and (melanoma or basal cell carcinoma or squamous cell carcinoma or skin cancer)”- without any restriction. We selected the studies according to the following inclusion criteria: 1) randomized controlled trials, cohort studies, or case-control studies; 2) studies comparing PDE5 inhibitors with placebo or non-PDE5 inhibitors; 3) follow-up for at least 52 weeks (not applicable to case-control studies), due to the fact that little information relevant to cancer incidence was reported in studies of shorter duration; 4) reporting the outcomes of skin cancer. The primary outcome of interest was risk of melanoma, and secondary outcomes included basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). We excluded conference abstracts because they offer limited information with which to assess study quality, population, and outcomes.

Data extraction and quality assessment

We collected information on study design, drug use, study location, characteristics of participants, selection criteria, exposure definition, adjusted covariates, and outcomes of interest. Data on outcomes such as adjusted hazard ratio (HR), adjusted risk ratio (RR), and adjusted odds ratio (OR) were extracted if appropriate. The Cochrane risk of bias

tool for randomized trials¹¹ and the Newcastle-Ottawa quality-assessment scale (NOS) for observational studies¹² were used to assess quality. For NOS criteria, a maximum of nine stars would be allocated to the following domains: selection, comparability, and outcome/exposure, with higher scores indicating better quality. Two reviewers (H.T. and W.W.) independently extracted the data and assessed the quality of each study. Any disagreements were resolved by consensus or referral to a third reviewer (J.H.).

Statistical analysis

Adjusted ORs with 95% confidence interval (CI) were used to pool the outcome data for PDE5 inhibitor users compared with non-users. Although the effect measures differed between cohort studies (HR) and case-control studies (OR), they are relative measures, and these two effect estimates are close when the event rate is low (<5%)^{13, 14}. A random-effect meta-analysis model was used because of potential heterogeneity across studies. Statistical heterogeneity was further quantified using the I^2 statistic, with I^2 of <25%, ≥25% and <75%, and ≥75% indicating low, moderate, and high heterogeneity, respectively¹⁵. Furthermore, meta-regression and subgroup analyses were performed to determine whether the pooled estimates were affected by total dose (low dose vs. medium dose vs. high dose), region of study (Europe vs. USA), type of design (cohort study vs. case-control study), and specific PDE5 inhibitors (sildenafil vs. vardenafil vs. tadalafil). The definitions of low dose, medium dose, and high dose in each study are presented in **Supplemental Table 1**. A sensitivity analysis omitting each study successively and a cumulative meta-analysis by order of publication year were carried out to assess the robustness of our findings. In addition, publication bias for risk of melanoma was assessed using Begg's and Egger's tests, as well as visual inspection of

the funnel plots. All statistical analyses were performed with STATA (Version 14; Stata Corp., College Station, TX).

RESULTS

Study selection and study characteristics

Of 294 citations retrieved from electronic databases, three cohort studies^{5, 7, 8} and two case-control studies^{6, 9} met the eligibility criteria and were included in our meta-analysis, involving a total of 998,456 participants (**Fig 1**). No randomized studies were identified. The characteristics of the included studies are presented in **Table 1**. In total, 15,916 incident melanoma cases came from five studies, 46,785 incident BCC cases came from four studies, and 637 incident SCC cases came from two studies. However, two studies were performed using UK Clinical Practice Research Datalink (CPRD)^{7, 8}, which might have some overlapping patients. Both studies were included because they differed in study design and selection criteria. One study used the cohort study design including male patients newly diagnosed with erectile dysfunction aged ≥ 40 years from 1998 to 2014 and those without any type of skin cancer diagnosis, who were never prescribed PDE 5 inhibitors before cohort entry⁷. The other study used a matched cohort study design including male patients without any prior cancer diagnosis aged ≥ 18 years from 1999 to 2014 and those who were prescribed a PDE5 inhibitor as the exposures, matched to four unexposed controls⁸. The included studies were of adequate quality, with more than seven stars out of nine in the NOS quality assessment (**Supplemental Table 2**).

Meta-analysis

The meta-analysis demonstrated that PDE5 inhibitors increased the risk of melanoma (adjusted OR 1.12, 95% CI 1.03-1.21, $I^2 = 49.1\%$) and BCC (adjusted OR 1.14, 95% CI

1.09-1.19, $I^2 = 49.5\%$), with moderate heterogeneity. In contrast, there was no evidence of any increased risk of SCC among PDE5-inhibitor users (adjusted OR 1.04, 95% CI 0.78-1.37, $I^2 = 16.9\%$) (**Fig 2**).

Furthermore, meta-regression and subgroup analyses were performed to examine the source of heterogeneity (**Table 2**). The subgroup analysis by dose showed that the adjusted risk of melanoma was 1.06 (95% CI 0.95-1.19, $I^2 = 60.2\%$) for low-dose users, 1.11 (95% CI 1.05-1.18, $I^2 = 0\%$) for medium-dose users, and 1.08 (95% CI 1.00-1.18, $I^2 = 13.3\%$) for high-dose users (**Supplemental Fig 1**). Additionally, our meta-regression analysis indicated that the risk was not statistically different across the three dose subgroups (P for interaction = 0.62). Another subgroup analysis by region of study found a significantly increased risk of melanoma in the studies performed in Europe (adjusted OR 1.13, 95% CI 1.06-1.21, $I^2=0\%$), but not in the USA (adjusted OR 1.37, 95% CI 0.64-2.93, $I^2=76.0\%$) (**Supplemental Fig 2**). Use of PDE5 inhibitors was significantly associated with increased risk of melanoma in cohort studies (adjusted OR 1.19, 95% CI 1.01-1.40, $I^2=33.2\%$), but not in case-control studies (adjusted OR 1.09, 95% CI 0.98-1.20, $I^2=63.3\%$) (**Supplemental Fig 3**). In addition, no individual PDE5 inhibitor was significantly associated with increased risk of melanoma (**Supplemental Fig 4**). There was no significant difference between these subgroups (P for interaction > 0.05).

Sensitivity analysis and publication bias

The significant association between PDE5 inhibitor use and increased risk of melanoma remained robust in the sensitivity analysis when each study was successively omitted (**Supplemental Fig 5**). When one of the studies based on the UK CPRD was excluded,

the result of excluding the study performed by either Lian Y *et al.*⁷ (OR, 1.11; 95%CI, 1.01 to 1.22) or Matthews A *et al.*⁸ (OR, 1.11; 95%, 1.00 to 1.24) was similar to primary result. Our cumulative meta-analysis ordered by publication year indicated that PDE5 inhibitor use was associated with a slight increase in risk of melanoma, and the point estimate gradually moved towards the null as the CI narrowed (**Supplemental Fig 6**). There was no evidence of substantial publication bias based on the Egger's test ($P = 0.12$), Begg's test ($P = 0.09$) or visual inspection of the funnel plot (**Supplemental Fig 7**).

DISCUSSION

Our meta-analysis of five observational studies involving a large number of total participants and incident cases of skin cancer provides evidence that PDE5 inhibitor use is slightly but significantly associated with increased risk of melanoma and BCC, but not SCC. For risk of melanoma, there was no evidence of dose-dependent association with PDE5 inhibitor use. Based on the results of a meta-regression, no other pre-specified factors (study design, study region, and type of PDE5 inhibitor) significantly affected the overall results. A significantly increased risk of melanoma was found in European populations, but not in US populations. Our cumulative meta-analysis indicated a weak association, and the point estimate gradually moved towards the null. Furthermore, the sensitivity analysis omitting each study successively confirmed the robustness of our results. However, our results should be interpreted with caution due to heterogeneity across studies.

Several laboratory studies have reported that PDE5 inhibitors might promote melanoma cell growth and migration through activation of the cGMP pathway²⁻⁴. Recently, a cGMP-dependent mitogen-activated protein kinase (MAPK) pathway was identified in melanoma cells as the link between sildenafil use and increased melanoma risk⁴. Nevertheless, laboratory studies are warranted to examine the effect of the intermittent use of PDE5 inhibitors on inducing irreversible changes in gene expression and promoting melanoma development⁵. However, evidence of an epidemiological association between the use of PDE5 inhibitors and risk of melanoma remains inconsistent. One study showed that PDE5 inhibitor use was not associated with overall elevated risk of melanoma, though the risk was significantly higher among those who

had received seven or more prescriptions or ≥ 25 pills⁷. Our findings did not indicate a strong dose-response relationship between the use of PDE5 inhibitors and risk of melanoma. Therefore, we must interpret this association with caution.

We found a significantly increased risk of melanoma associated with PDE5 inhibitors only in European populations, but not in U.S. populations. It should be noted that an increased risk of melanoma was observed in U.S. populations, but it did not reach statistical significance. Factors that might explain the differences in risk of melanoma associated with PDE5 inhibitor use among these populations include socioeconomic and cultural differences.

Furthermore, the association between PDE5 inhibitor use and risk of melanoma might be influenced by potential confounders. Matthews A *et al.* showed that this significant association might be confounded by greater sun exposure among users of PDE5 inhibitors⁸. Their post hoc analysis showed that solar keratosis was significantly associated with PDE5 inhibitor use, which indicated that men with higher sun exposure were more likely to take PDE5 inhibitors⁸. However, further meta-analysis was limited by lack of data on sun exposure in individual studies. Additionally, our meta-analysis found a similar increase in risk of BCC, but there was no increase in the risk of SCC. Melanoma is more closely related to intermittent sun exposure, whereas non-melanoma skin cancer is more related to chronic sun exposure. Further studies are necessary to clarify the potential effect modification and confounding by sun exposure. In addition, a study by Loeb *et al.* indicated that PDE5 inhibitor users had higher educational levels and annual income, which were also significantly associated with melanoma risk. Finally, the study by Pottegård A *et al.* found an increased incidence of lower stage/grade of melanoma

among PDE5 inhibitor users than non-users, which suggested that the slightly elevated risk of melanoma might be attributable to more health-seeking behaviors, resulting in earlier detection⁹. The causality remains elusive, and further well-conducted large-scale prospective studies or randomized trials are still needed to confirm our findings.

Our study has several strengths. First, this is the first meta-analysis to address the association between PDE5 inhibitors and risk of melanoma by including all relevant literature to date. Second, we performed subgroup analysis, sensitivity analysis, and cumulative meta-analysis to confirm the robustness of our findings. We also acknowledge that our meta-analysis has several limitations. First, no randomized controlled trials were identified, despite a systematic search of electronic databases. Second, doses were stratified differently across studies; this might contribute to the observed heterogeneity, which might also have affected the results of our subgroup analysis by dose. Third, two studies were performed in the same database over the same time period, which might result in some overlapping patients^{7, 8}. Both studies were included due to the fact that they differed in study design and patient selection. Furthermore, excluding each study produced results similar to the primary results. Fourth, we were unable to determine the potential confounding effect of ultraviolet radiation exposure, skin type, or family history of melanoma. In addition, adjustment among studies for other confounders (e.g., age, immunosuppression, social economic status, and marital status) was inconsistent. Finally, our meta-analysis detected statistical heterogeneity, which might be due (at least in part) to the study of different geographic regions.

In conclusion, some evidence suggests that use of PDE5 inhibitors may be slightly associated with increased risk of melanoma and BCC, but not SCC.

Further large, well-conducted prospective studies with clear definitions of dose and duration of PDE5 inhibitors and adequate adjustment for potential confounders (e.g., ultraviolet exposure) are required for confirmation.

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Abbreviations used:

PDE5: phosphodiesterase type 5

cGMP: cyclic guanosine-3', 5'-monophosphate

MAPK: mitogen-activated protein kinase

OR: odds ratio

HR: hazard ratio.

CI: confidence interval

BCC, basal cell carcinoma

SCC, squamous cell carcinoma

NOS, Newcastle-Ottawa quality-assessment scale

Figure legends:

Fig 1. Flow chart of the identification of eligible studies

Fig 2. Meta-analysis of the association between phosphodiesterase type 5 inhibitor use and risk of skin cancer

1 **Table 1.** Characteristics of included studies

Study	Study design and data source	No. of participants	Age (years)	Selection criteria	Exposure definition	Non-exposure definition	Adjusted covariate
Li WQ et al. (2014) [5]	Prospective cohort study; Health Professionals Follow-up Study (HPFS); USA, 1986-2000	Sildenafil: 727; Non-sildenafil: 14,185	Mean: 64	Men aged 40-75 years, who completed a baseline questionnaire on medical history and lifestyle practices	Sildenafil	Unexposed to sildenafil	Age, body mass index, smoking, physical activity, childhood reaction to sun, times of sunburns, mole count, hair color, family history of melanoma, sun exposure, UV index, as well as other treatment for erectile function problems.
Loeb S et al. (2015) [6]	Nested case-control study; Swedish Prescribed Drug Register, Swedish Melanoma Register, and other health care registers and demographic databases; Sweden, 2006-2012	PDE5 inhibitors: 2,148; Non-PDE5 inhibitors: 22,242	Median: 73	Incident melanoma cases without other cancers were randomly matched to 5 cancer-free controls	Prescribed PDE5 inhibitors since 2006	Not-prescribed PDE5 inhibitors	CCI, marital status, educational level and disposable income
Lian Y et al. (2016) [7]	Prospective cohort study; UK Clinical Practice Research Datalink (CPRD); UK, 1998 - 2014	PDE5 inhibitors: 58,732; Non-PDE5 inhibitors: 84,611	Mean: 59	Erectile dysfunction patients aged ≥40 years, have at least 1 year of baseline medical history, and have never been prescribed PDE5 inhibitors at any time before cohort entry; excluded patients diagnosed with any type of skin cancer before cohort entry	PDE5 inhibitors; at least 1 year of follow-up after cohort entry	Unexposed until the year after the first PDE5 inhibitor prescription	Age, year of cohort entry, alcohol-related disorders, smoking status, BMI, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, CCI, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking-related variables
Matthews A et al. (2016) [8]	Prospective matched cohort study; UK Clinical Practice Research Datalink	PDE5 inhibitors: 145,104; Non-	Median: 57	All adult men initiating a PDE5 inhibitor and with no prior cancer	PDE5 inhibitors; at least 1 year of follow-up	Unexposed to PDE5 inhibitors at least 1 year	Age, alcohol use, number of consultations in year before index date, BMI category, alcohol use, smoking status

	(CPRD);UK,1999-2014	PDE5 inhibitors: 560,933		diagnosis were identified and matched on age, diabetes status, and general practice to up to four unexposed controls	prior to the first prescription record	of follow-up prior to the index date of the exposed patient	
Pottegård A et al. (2016) [9]	Case-control study; Danish Nationwide Health Registries (DNHR); Denmark, 2000-2012 Kaiser Permanente Northern California (KPNC) electronic health records; USA, 2000-2014	DNHR: PDE5 inhibitors: 4,603; Non-PDE 5 inhibitors: 72,892 KPNC: PDE5 inhibitors: 6033; Non-PDE 5 inhibitors: 26,246	NR	Men with histologically verified melanoma (cases) matched on birth year to 10 cancer-free controls	Two or more filled prescriptions for any PDE5 inhibitors prior to the index date	None or one filled prescription of any PDE5 inhibitors	Age and calendar time, use of oral steroids, weak/moderate topical steroids, strong/very strong topical steroids, thiazides, beta-blockers, angiotensin-II receptor blockers, low-dose aspirin (only in the DNHR), non-aspirin non-steroidal anti-inflammatory drugs, antidepressants, and statins; (b) diagnoses of non-melanoma skin cancer, type 1 or type 2 diabetes, chronic obstructive pulmonary disease, alcohol-related disease, and moderate to severe renal disease; and (c) highest education achieved (in the DNHR) and socioeconomic level based on the US Census block of residence (in the KPNC database).

2 PDE5, phosphodiesterase type 5; NR, not reported. UV, ultraviolet; BMI, body mass index; CCI, Charlson comorbidity index

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5 **Table 2.** Subgroup analysis of association between PDE5 inhibitors and risk of
 6 melanoma

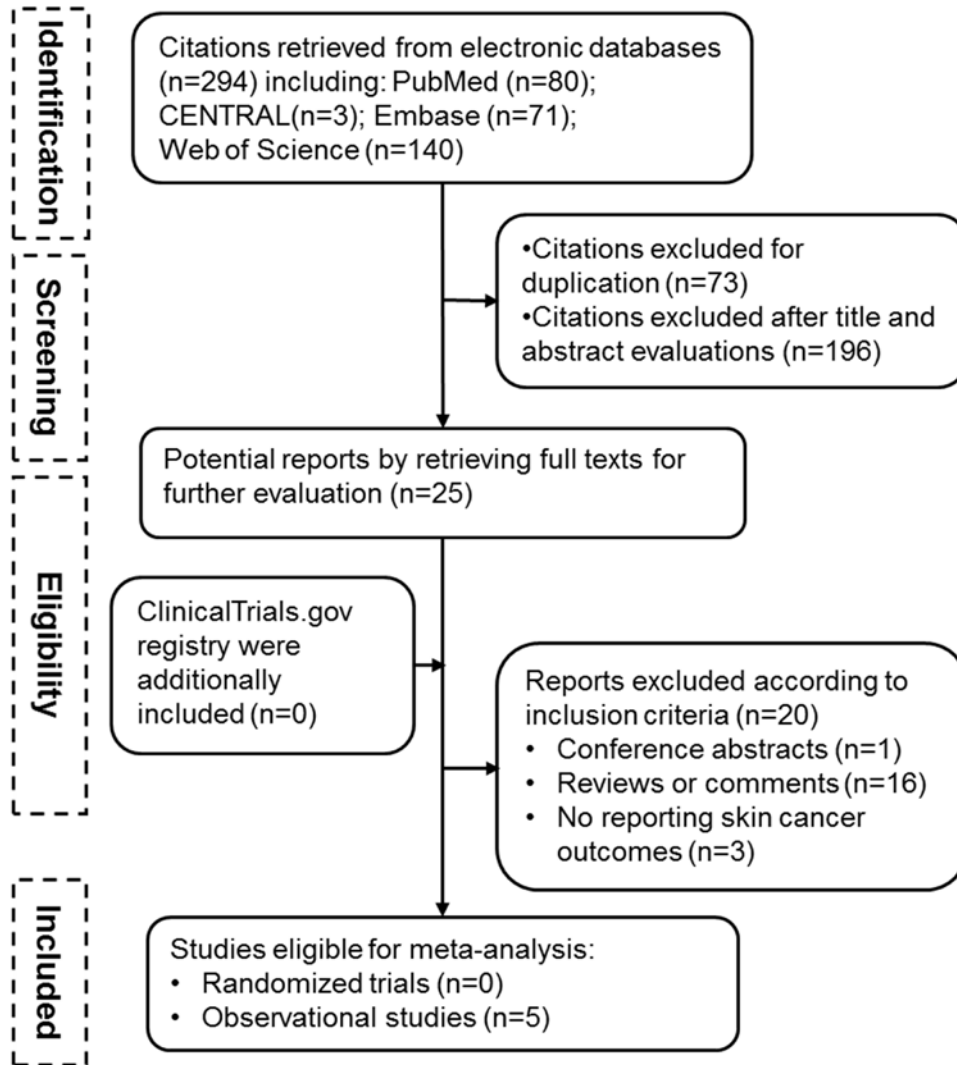
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		Number of studies	Adjusted odds ratio (95%CI)	I ² (%)	P for interaction
Overall		5	1.12 (1.03,1.21)	49.1	-
Total dose					
	Low dose	4	1.06 (0.95, 1.19)	60.2	0.62
	Medium dose	4	1.11 (1.05, 1.18)	0	
	High dose	4	1.08 (1.00, 1.18)	13.3	
Region of study					
	Europe	4	1.13 (1.06, 1.21)	0	0.35
	USA	2	1.37 (0.64, 2.93)	76	
Design of study					
	Cohort study	3	1.19 (1.01, 1.40)	33.2	0.46
	Case-control study	2	1.09 (0.98, 1.20)	49.1	
Type of PDE5 inhibitor					
	Sildenafil	3	1.08 (0.97, 1.21)	49.4	0.30
	Vardenafil	1	1.03 (0.91, 1.17)	-	
	Tadalafil	1	1.06 (0.88, 1.28)	-	
	Vardenafil or tadalafil	1	1.16 (0.99, 1.36)	-	

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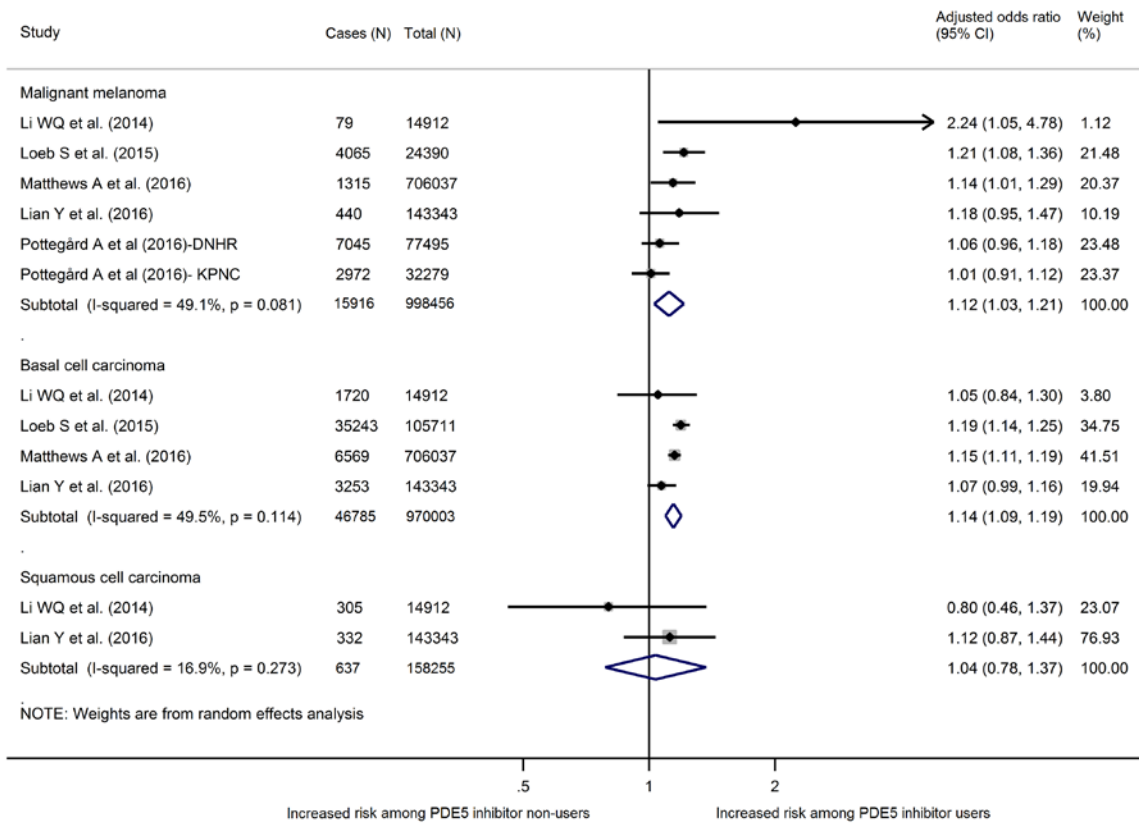
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