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No Causal Link between Phosphodiesterase Type 5 Inhibition and Melanoma

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Purpose: To examine the association between phosphodiesterase type 5 (PDE5) inhibitor use and melanoma by 1) conducting a systematic review of observational studies; and 2) determining if low PDE5A gene expression in human melanoma correlated with decreased overall survival.

Materials and Methods: A systematic search of observational studies examining the association between PDE5 inhibitor use and melanoma was performed through ClinicalTrials.gov, the Cochrane Library, EMBASE, PubMed, and Web of Science databases, and seven eligible studies were identified. PDE5A gene expression was analyzed with RNA sequencing data from 471 human melanoma samples obtained from The Cancer Genome Atlas.

Results: Four studies reported a positive association between PDE5 inhibitor use and melanoma, and three studies found no correlation. RNA sequencing data analysis revealed that under-expression of the PDE5A gene did not impact clinical outcomes in melanoma.

Conclusions: There is currently no evidence to suggest that PDE5 inhibition in patients causes increased risk for melanoma. The few observational studies that demonstrated a positive association between PDE5 inhibitor use and melanoma often failed to account for major confounders. Nonetheless, the substantial evidence implicating PDE5 inhibition in the cyclic guanosine monophosphate (cGMP)-mediated melanoma pathway warrants further investigation in the clinical setting.

Keywords: Melanoma; Phosphodiesterase 5 inhibitors; Sildenafil citrate; Tadalafil; Vardenafil dihydrochloride

INTRODUCTION

Ever since the introduction of sildenafil 20 years ago, phosphodiesterase type 5 (PDE5) inhibitors have become the mainstay therapy in the treatment of penile erectile dysfunction (ED), which can be severely limiting in an estimated 5% to 20% of men worldwide [1]. PDE5 inhibitors work by blocking the PDE5 enzymatic activity that degrades cyclic guanosine monophosphate (cGMP), a smooth muscle relaxant found in the corpus cavernosum of the penis, thereby promoting increased penile smooth muscle relaxation, blood flow, and subsequent enhancement of the male erectile response [2].

The link between PDE5 and melanoma was first al-

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luded to in 1993 when Drees et al [3] isolated a cGMP-specific PDE isoenzyme in B16 mouse malignant melanoma cells. Subsequent studies confirmed PDE5 expression and activity in melanoma-associated antigens in human malignant melanoma cells [4]. Furthermore, PDE5 inhibitors were shown to stimulate melanin synthesis [5], which significantly promoted the development of melanomas [6]. And just recently, a histopathologic study found a unique correlation between markedly dilated vessels and melanoma growth in two patients with long-standing sildenafil use, hinting at a potential physiologic mechanism [7].

Possibly, the most detailed mechanism was proposed by Arozarena et al [8], who discovered that the melanoma-associated ^{V600}EBRAF mutation promoted melanoma metastasis by downregulating PDE5 protein expression. Their findings were particularly compelling given that BRAF mutations are implicated in over 50% of melanomas [9]. In their study, inhibition of PDE5 elevated cGMP and cytosolic Ca^{2+} levels, which stimulated actin-myosin contractility and melanoma cell invasion. Interestingly, the response was specific to BRAF mutant melanoma cells, as the same effect was not seen in NRAS mutant melanoma cells. These investigators, however, did not find evidence that pharmacologic PDE5 inhibition (*i.e.*, sildenafil, tadalafil, or vardenafil) further augmented melanoma invasiveness in BRAF mutant melanoma cells, as PDE5 protein was already downregulated in these cells.

A second signaling pathway was further elucidated by Dhayade et al [10], who confirmed that activation of the cGMP pathway by PDE5 inhibition promoted melanoma cell growth and migration in a p44/42 MAPK-dependent manner. In addition, they found that sildenafil administration in mice promoted the growth of existing melanomas, which supports their theory that release of the 'PDE5 brake' on the cGMP growth-promoting pathway generates more proliferative melanoma tumors [11].

Paradoxically, there also exists evidence that PDE5 inhibition may have a protective role in preventing melanoma formation by promoting antitumor immunity and manipulating the tumor microenvironment [12]. Myeloid-derived suppressor cells (MDSCs) enhance tumor survival and proliferation through a multitude of different pathways, including suppression of antitumor T cell activity [13]. Three clinical trials found that oral administration of tadalafil, a PDE5 inhibitor, reduced MDSCs and restored antitumor T cell immunity in patients with head and neck squamous cell carcinoma [14,15] and metastatic melanoma [16]. Although overall increase in survival was not demonstrated, PDE5 inhibition may represent a novel adjunct to immunotherapy.

Given the widespread popularity of PDE5 inhibitors, there has been growing interest in the recent decade to further clarify the potential risks and long-term side effects of PDE5 inhibitor use. Li et al [17] was the first group to report an association between sildenafil use in USA males and increased risk of developing melanoma. Since then, eight more studies have attempted to address the same clinical question with varying results [18-24]. Therefore, we conducted a systematic review of the current literature to investigate the association between PDE5 inhibitor use and malignant melanoma. We also sought to determine if under-expression of the *PDE5A* gene translates into worse clinical outcomes for melanoma patients.

MATERIALS AND METHODS

1. Search strategy and eligibility criteria

A systematic search was performed in ClinicalTrials.gov, the Cochrane Library, EMBASE, PubMed, and Web of Science databases to identify randomized controlled trials or observational studies published up to May 2, 2018 that evaluated the association between PDE5 inhibitor use and risk of developing melanoma. We used a combination of the following search terms: 'avanafil', or 'lodenafil', or 'mirodenafil', or 'PDE5', or 'phosphodiesterase type 5', or 'phosphodiesterase-5', or 'sildenafil', or 'tadalafil', or 'udenafil', or 'vardenafil', AND 'melanoma'.

Studies were eligible for our systematic review if they met the following inclusion criteria: 1) were original articles in peer-reviewed scientific journals; 2) were randomized controlled trials or observational studies; 3) defined PDE5 inhibitor use as the primary exposure of interest; 4) included a control group of PDE5 inhibitor non-users; 5) reported development of malignant melanomas as the primary outcome of interest; and 6) calculated odds ratio or hazard ratio with 95% confidence interval. We excluded irrelevant studies, review articles, letters to editors, comments, duplicate publications, and experimental studies in animals or cell lines.

2. Data extraction and quality assessment

Two authors (JZW and EM) independently performed the literature search, data extraction, and quality assessment. Discrepancies were resolved by consensus. The extracted data included the following information where available: name of authors, study period, study design, country, data source, number of participants, patient characteristics, defined exposure of interest, defined control group, defined outcome of interest, and multivariate adjusted factors. Each study was evaluated for quality with the Newcastle–Ottawa scale (NOS) for a maximum of nine points on the following criterion: selection, comparability, and outcome [25].

3. Kaplan–Meier analysis

To assess the effect of *PDE5A* gene expression on overall survival in melanoma patients, a proportional hazards regression model was constructed using Kaplan–Meier analysis with the R package 'Survival' (Therneau T. A package for survival analysis in S. 2.38. 2015; https://cran.r-project.org/web/packages/survival/index.html). Tumor RNA sequencing data was generated from cutaneous melanoma samples of all tumor stages (0–IV), from 470 patients (180 females and 290 males) in the publicly available Genomic Data Commons (GDC) data portal [26]. A resulting step function was plotted as cumulative survival against time (Fig. 1A). We further stratified our data analysis to include only patients relevant to our study population (*i.e.*, male patients ages 18–91 years) (Fig. 1B). For this analysis, melanoma patients were divided equally into either the lower and upper 50% with regards to their *PDE5A* gene expression.

RESULTS

1. Study selection and characteristics

The initial literature search generated 223 articles, of which 50 were from PubMed, 118 from EMBASE, 55 from Web of Science, and 0 from the Cochrane Library and ClinicalTrials.gov. After removing duplicate citations, the remaining 131 articles were screened by their titles and abstracts to filter out 1) irrelevant articles; 2) non-human studies; or 3) reviews and letters. No randomized controlled studies were identified. Nine observational studies were found and underwent full review. Among these, one did not report development of malignant melanoma as the primary outcome of interest, and two did not include adequate information regarding their control groups. Six articles, including one conference abstract, were included in our final review after meeting our eligibility criteria (Fig. 2).

Of the six articles, we identified four independent case-control studies [18,21,22] and three cohort studies [17,19,20]. Both Lian et al [19] and Matthews et al [20] conducted their studies using the same Clinical Practice Research Datalink (CPRD, UK) data source, but with different selection criteria and research protocol. One article included two parallel case-control

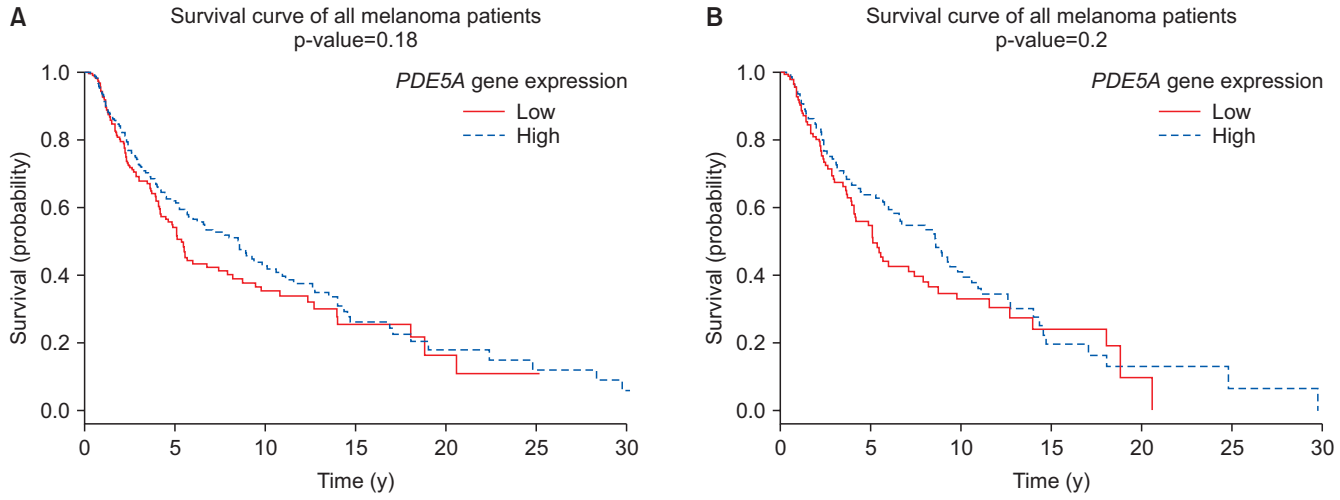

Fig. 1. Kaplan–Meier survival curve for differential expression levels of *PDE5A* gene in (A) 470 patients (180 females and 290 males) with a diagnosis of melanoma at any tumor stage (0–IV), ages 14–91 years; and (B) specifically male melanoma patients (n=287) with a diagnosis of melanoma at any tumor stage (0–IV), ages 18–91 years. Melanoma prognosis unaffected by high or low *PDE5A* expression in patients, regardless of gender, age, or tumor stage.

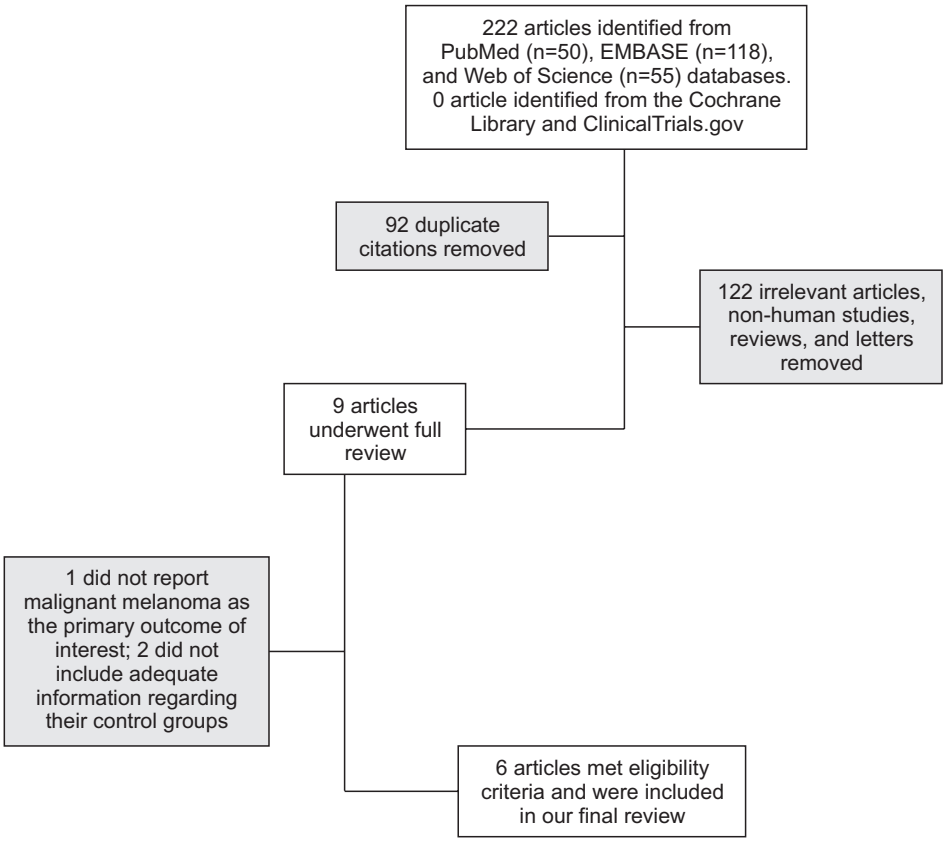

Fig. 2. Flowchart of our database search and identification of eligible studies.

studies using separate data sources from the Danish Nationwide Health Registries (DNHR, Denmark) and the Kaiser Permanente Northern California database (KPNC, USA) (Table 1) [21].

The seven independent studies reported 16,257 melanoma cases out of 1,009,762 male participants from either the USA or European countries. Mean and median ages of participants ranged from 57 to 72 years, and all studies were adjusted at the very minimum for age. Participant data from Europe was collected from national registries within their respective home country [19-21]; Lian et al [19] further refined participant selection from registry data to include only males with preexisting ED diagnoses. Of the studies within the US, Li et al [17] collected data from self-reported surveys completed by male health professionals while Pottegård et al [21] and Ma et al [22] collected data from large regional hospital network registries. Participant skin types were not specified in the studies, but Pottegård et al [21] excluded non-white participants in their KPNC case-control study, under the presumption that "<5% of melanomas are diagnosed in non-whites, and membership of KPNC is racially/ethnically diverse." The exposure of interest was PDE5 inhibitor use and the primary outcome of interest was a diagnosis of melanoma. All studies included a control group of PDE5 inhibitor non-users. The studies achieved NOS quality scores of 5 to 7 out of a maximum of 9 points.

2. No causal relationship between phosphodiesterase type 5 inhibitor use and melanoma

Four studies reported a positive association between PDE5 inhibitor use and melanoma that reached statistical significance [17,18,20,22]. Of the four studies that found a positive correlation, two acknowledged that confounding factors (*i.e.*, sun exposure) likely contributed to their findings [18,20]. Three studies found no correlation between PDE5 inhibitor use and melanoma [19,21], and no study concluded there was a proven causal relationship between PDE5 inhibitor use and melanoma (Table 2).

3. No association between *PDE5A* gene expression and melanoma prognosis

PDE5A gene expression was not associated with melanoma survival, regardless of age, tumor stage (0–IV) or gender (Fig. 1). Although *PDE5A*-expressing

Table 1. Study characteristics of observational studies

Study	Study period	Study design	Country	Data source	Patient characteristics	Average age (y)	Exposure definition	Outcome definition	Multivariate adjusted variable	NOS score[a]
Li et al (2014) [17]	2000–2010	Prospective cohort	USA	Health professionals' follow-up study	USA male health professionals	Mean 64.8	Self-reported sildenafil use in past 3 months	Melanoma diagnosis in EMR, reviewed by masked physicians	Age; BMI; smoking status; physical activity; childhood reaction to sun; no. of severe sunburns; mole count; hair color; family history of melanoma; sun exposure; UV index; other treatments for ED	7
Loeb et al (2015) [18]	2006–2012	Nested case-control	Sweden	Swedish national registries[b]	Swedish males	Median 70	PDE5 inhibitor prescription filled	Melanoma diagnosis in EMR	Age; CCI; marital status; educational level; disposable income	7
Lian et al (2016) [19]	1998–2015	Prospective cohort	UK	UK Clinical Practice Research Datalink	UK males with ED	Mean 59	PDE5 inhibitor prescription written	Melanoma diagnosis in EMR	Age; year of cohort entry; alcohol-related disorders; smoking status; BMI; precancerous skin lesions; presence of nevi; immunosuppression, use of antiparkinsonian drugs; CCI; no. of different drug classes used and no. of physician visits; other health-seeking-related variables[c]	5
Matthews et al (2016) [20]	1999–2014	Matched cohort	UK	UK Clinical Practice Research Datalink	UK males	Median 57	PDE5 inhibitor prescription code in EMR	Malignant melanoma diagnosis code in EMR, checked by consultant dermatologist	Age; diabetes status, length of medical history; BMI; smoking status; alcohol use; frequency of consultations	5
Pottegård et al (2016) [21]	2000–2012	Matched case-control	Denmark	DNHR[d]	Danish males	Median 61	Two or more PDE5 inhibitor prescriptions filled	Primary invasive melanoma diagnosis confirmed on histology	Age; date prescriptions filled; medications used; diagnoses of non-melanoma skin cancers and other comorbidities (*i.e.*, diabetes, COPD, renal disease, etc); alcohol-related disease; highest education level (DNHR-specific)	7
Pottegård et al (2016) [21]	2000–2014	Matched case-control	USA	KPNC databases[e]	White USA males	Median 64	Two or more PDE5 inhibitor prescriptions filled	Primary invasive melanoma diagnosis confirmed on histology	Same as DNHR study, except socioeconomic levels based on US Consensus block of residence	7
Ma et al (2017) [22]	1998–2010	Population based case-control	USA	Rochester Epidemiology Project Database	USA males	Mean 68–71	Sildenafil prescription in EMR	Malignant melanoma diagnosis in EMR	Age; race; prior sildenafil use and date; family history of melanoma; history of ED; cardiac history; non-skin cancer; nonmelanoma skin cancers; tobacco use; immunosuppression	5

NOS: Newcastle–Ottawa Scale, EMR: electronic medical record, BMI: body mass index, UV: ultraviolet, ED: erectile dysfunction, PDE5: phosphodiesterase 5, CCI: Charlson Comorbidity Index, DNHR: Danish Nationwide Health Registries, COPD: chronic obstructive pulmonary disease, KPNC: Kaiser Permanente Northern California.
[a]The NOS is assessed on a 9-point scale based on the following criterion: selection, comparability, and outcome. [b]Swedish national registries include the Swedish Prescribed Drug Register, Swedish Melanoma Register, Prostate Cancer Data Base Sweden, and Swedish Cancer Registry. [c]Other health-seeking-related variables include influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing. [d]DNHR include the Danish Cancer Registry, National Prescription Registry, National Registry of Patients, Danish Education Registries, and Danish Civil Registration System. [e]KPNC databases include the KPNC Registry, KPNC pharmacy database, and other KPNC electronic medical record databases.

Table 2. Risk assessment between phosphodiesterase 5 inhibitor exposure and melanoma

Study	No. of total participants	No. of melanoma cases (no. exposed; no. of controls)	Total no. exposed	Total no. of controls	Multivariate adjusted risk assessment HR or OR (95% CI)
Li et al (2014) [17]	25,848	142 (14 exposed; 128 controls)	1,378	24,470	HR: 1.84 (1.04–3.22)
Loeb et al (2015) [18]	24,390	4,065 (435 exposed; 3,630 controls)	2,148	20,325	HR: 1.21 (1.08–1.36)
Lian et al (2016) [19]	142,983	440 (328 exposed; 112 controls)	58,372	84,611	HR: 1.18 (0.95–1.47)
Matthews et al (2016) [20]	706,037	1,315 (321 exposed; 994 controls)	145,104	560,933	HR: 1.14 (1.01–1.29)
Pottegård et al (2016) [21][a]	77,495	7,045 (448 exposed; 6,597 controls)	4,603	70,450	OR: 1.06 (0.96–1.18)
Pottegård et al (2016) [21][b]	32,279	2,972 (568 exposed; 2,404 controls)	6,033	29,307	OR: 1.01 (0.91–1.12)
Ma et al (2017) [22]	730	278 (50 exposed; 228 controls)	99	452	OR: 2.38 (1.49–3.81)

HR: hazard ratio, OR: odds ratio, CI: confidence interval.
[a]Danish Nationwide Health Registries (DNHR) include the Danish Cancer Registry, National Prescription Registry, National Registry of Patients, Danish Education Registries, and Danish Civil Registration System. [b]Kaiser Permanente Northern California (KPNC) databases include the Kaiser Permanente Northern California Cancer Registry, KPNC pharmacy database, and other KPNC electronic medical record databases.

stromal cells and immune cells might also be present within the melanoma samples, there was no overwhelming evidence at the bulk tumor gene expression level suggesting that *PDE5A* gene expression is linked to melanoma.

DISCUSSION

Li et al [17] was the first study to report a positive association between self-reported sildenafil use and melanoma in a cohort of 25,848 USA male health professionals. They did note that sildenafil users were on average older, more obese, and more likely to have a history of severe or blistering sunburns, all of which are known risk factors for developing melanoma [27]. However, a significant association persisted even after they adjusted for a variety of common risk factors, such as age, body mass index, smoking, physical activity, hair color, sun exposure, sunburns, number of moles, and family history of melanoma. The primary disadvantage of the study was that the disease outcome was so rare, as only 142 melanoma cases were identified, of which only 14 participants reported as having used sildenafil in the past. The study might also have been subject to information or recall bias, as those who diligently self-reported medication may also engage in more health-seeking behaviors (*i.e.*, skin cancer screenings), which can lead to an increased number of melanoma diagnoses [28].

The findings from Li et al's 2014 study [17] prompted Loeb et al [18] to further investigate a possible causal relationship between PDE5 inhibitor use and melanoma. They conducted a large national nested case-control study using comprehensive population-based data from the Swedish national registries. The registries included detailed information on melanoma staging and location, medications prescribed and filled, socioeconomic factors (*i.e.*, education, income, and marital status), and presence of other comorbidities (*i.e.*, prostate cancer and basal cell carcinoma [BCC]). In this study, researchers included 435 melanoma cases, which was 30 times more than those in Li's original study [17]. Their results were consistent with the 2014 study, as they also found an increased risk for melanoma amongst users.

In order to fulfill Hill's Criteria of Causality [29] and ascertain whether or not PDE5 inhibitors actually 'caused' melanoma, however, Loeb et al [18] examined the dose-response relationship and specificity between PDE5 inhibitor use and melanoma. Interestingly, they only found a pronounced risk in men who filled a single prescription, rather than in men who filled 2–5 prescriptions or even ≥6 prescriptions. There was also no evidence to suggest that vardenafil or tadalafil, both of which have longer half-lives compared to sildenafil, further increased the risk of melanoma, arguing against a dose-response relationship. Furthermore, they

found a correlation between PDE5 inhibitors and BCC, a disease that has not yet been linked to cGMP signaling, which reduced the specificity of the melanoma association. A major potential confounder unaccounted for in this case was ultraviolet (UV) sun exposure, as it is a known risk factor for both BCC and melanoma [30] (*i.e.*, if the PDE5 inhibitor cohort also had more BCCs, they may also have had more sun exposure). Lastly, they found that PDE5 inhibitor use most significantly increased the prevalence of stage 0 and I melanoma, and 'not' the more advanced types (stages II–IV), which contradicts the theory that PDE5 inhibition promotes aggressive melanoma invasion [8,11].

Matthews et al [20] conducted the largest matched cohort study to date, by analyzing UK national registry data on 706,037 men. They found a slightly elevated risk for melanoma in men with ≥1 PDE5 inhibitor prescriptions. Like Loeb et al [18], they also found a positive association between PDE5 inhibitors and BCC. Although data on UV sun exposure was not collected, post-hoc analysis found overwhelming evidence linking PDE5 inhibitors to prior solar keratoses, a known marker for sun exposure [31]. PDE5 inhibitor users were also more likely to have solar keratoses 'before' receiving their first prescription, suggesting that users were more likely to have excessive sun exposure at baseline compared to non-users. There was also no evidence linking cumulative PDE5 inhibitor exposure to melanoma, arguing against a dose-response relationship.

Since then, three more conference abstracts have published positive correlations between PDE5 inhibitor use and melanoma [22-24], of which only one was eligible for this review. Ma et al [22] conducted a small case-control study that followed 730 men from the Rochester Epidemiology Project (REP) database, a regional hospital network registry. Similar to Li et al's study [17], however, the small subpopulation of 278 melanoma cases limited the strength of this study. While they did not find a statistical difference in melanoma staging, they did find a higher association with lentigo maligna melanoma amongst users. Interestingly, lentigo maligna melanoma is a subtype of melanoma linked to older age and chronic sun exposure [32], further corroborating the theory that sun exposure may be a major confounder.

Contrary to the studies above, three studies in our search reported no association between PDE5 inhibitors and melanoma [19,21]. Lian et al [19] and Matthews et al [20] both utilized the same UK national registry data for their prospective cohort studies; Lian et al [19], however, implemented more stringent patient eligibility criteria, limiting the inclusion of subjects to males with a diagnosis of ED. They restricted their study population to 1) reduce surveillance bias, as PDE5 inhibitor users tend to have higher education levels, which correlates to more skin cancer screenings [33,34]; and 2) reduce confounders like sedentary lifestyle behaviors and cardiometabolic comorbidities (*i.e.*, obesity, diabetes, and cardiovascular disease) linked to both ED and melanoma [35,36]. Lian et al's analysis [19] was not able to find an association with BCC amongst users, despite failing to control for the potential confounder of sun exposure proposed by Matthews et al [20]. This suggests that confounders unrelated to sun exposure (*i.e.*, lifestyle or health-seeking behaviors) may play a larger role in the PDE5 inhibitor melanoma association.

Lastly, Pottegård et al [21] conducted two independent case-control studies using separate patient populations (Denmark and Northern California), and found no association between PDE5 inhibitors and melanoma in either study. Consistent with Loeb et al's findings [18] regarding melanoma staging, Pottegård et al [21] did find slightly elevated risk of localized (stage 0 or I) melanoma in their Dutch population, but not with metastatic disease. This association, however, disappeared completely when health-seeking markers (*i.e.*, education and frequency of ambulatory visits) were accounted for, reducing surveillance bias. Although they found no increased melanoma risk amongst users in general, high cumulative use (200–500 tablets) of PDE5 inhibitors increased melanoma risk in their Dutch population. This observation was mutual between Lian et al [19], who found a modest increase in risk with ≥7 prescriptions (median=20 prescriptions). These isolated findings may be a reflection of traits found in a particular patient subgroup (*i.e.*, behavioral traits or polypharmacy) and do not strongly support a dose-response relationship between PDE5 inhibitors and melanoma. Not surprisingly, Pottegård et al [21] found that the increased risk disappeared in Denmark males taking ≥500 tablets.

Our systematic review was limited to observational studies, which are inferior to randomized controlled trials in determining a causative relationship between

exposures and outcomes. We also included one of three conference abstracts in our review, which often omit critical information about study methods; therefore making them difficult to assess for bias. There is also a potential for publication bias, as some authors received funding from pharmaceutical companies producing PDE5 inhibitors [18,20,21]. Additionally, several studies were limited to western men from countries with a homogenous population (*i.e.*, Denmark or Sweden) [18,21] or Caucasian men [21], which reduces the applicability of the studies to more diverse populations.

And finally, from the animal models described by Arozarena et al [8] and Dhayade et al [10], one would predict that low *PDE5A* gene expression in melanoma would impart poor survival. However, our gene expression analysis of GDC data did not support this. Although our analysis provided compelling evidence against the role of *PDE5A* gene in dictating clinical outcomes in melanoma patients, it does not exclude the possibility that PDE5 may still have a role in the development of new melanomas.

CONCLUSIONS

At present, there lacks evidence to support that PDE5 inhibitor use causes increased risk for melanoma, and there is only minimal evidence to support the association between the two. A consistent dose-response relationship has not been well established, and the concurrent association between users and BCC in several studies reduces the specificity of the association with melanoma. The studies that demonstrated a positive correlation often failed to account for major confounders such as sun exposure, health-seeking behaviors, or metabolic comorbidities that are linked to both PDE5 inhibitor use and melanoma. Finally, there is no strong molecular rationale for this association in human melanoma patients as *PDE5A* gene under-expression does not affect overall survival. Nonetheless, the substantial evidence implicating PDE5 inhibition in the cGMP-mediated melanoma progression remains an intriguing area of research, but should not alter clinical practice.

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Conceptualization: Wang JZ and Maverakis E. Supervision: Maverakis E. Writing–original draft–Wang JZ. Writing–review & editing–all authors. Methodology: Wang JZ, Merleev A, and Maverakis E. Formal analysis: Merleev A and Marusina A. Visualization: Wang JZ and Merleev A.

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