Phosphodiesterase Type 5 Inhibitors and the Risk of Melanoma Skin Cancer

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Abstract

Background: The association between phosphodiesterase type 5 inhibitors (PDE5-Is), drugs used in the treatment of erectile dysfunction (ED), and melanoma skin cancer is controversial.
Objective: To assess whether the use of PDE5-Is is associated with an increased risk of melanoma skin cancer.
Design, setting, and participants: Using the UK Clinical Practice Research Datalink, we assembled a cohort of men newly diagnosed with ED between 1998 and 2014 and followed until 2015. PDE5-I exposure was considered as a time-varying variable lagged by 1 yr for latency purposes.
Outcome measurements and statistical analysis: Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident melanoma associated with PDE5-I use overall and by number of prescriptions and pills received. Identical analyses were conducted for basal and squamous cell carcinoma, two cancers for which PDE5-related pathways are not thought to be involved.
Results and limitations: The cohort included 142 983 patients, of whom 440 were newly diagnosed with melanoma during follow-up (rate: 63.0 per 100 000 person-years). Compared with nonuse, PDE5-I use was not associated with an overall increased risk of melanoma (rates: 66.7 vs 54.1 per 100 000 person-years; HR: 1.18; 95% CI, 0.95–1.47). The risk was significantly increased among those who had received seven or more prescriptions and $\geq$25 pills (HR: 1.30 [95% CI, 1.01–1.69] and 1.34 [95% CI, 1.04–1.72], respectively). In contrast, there was no overall association with basal and squamous cell carcinoma, with an unclear association with numbers of prescriptions and pills received.
Conclusions: The use of PDE5-Is was not associated with an overall increased risk of melanoma skin cancer. The increased risks observed in the highest prescription and pill categories require further validation.
Patient summary: In this study, the use of phosphodiesterase type 5 inhibitors was not associated with an increased risk of melanoma skin cancer.

1. Introduction

Phosphodiesterase type 5 inhibitors (PDE5-Is), which include sildenafil, tadalafil, and vardenafil, are effective treatments for erectile dysfunction (ED) [1–3]. Although these drugs work by dilating blood vessels, laboratory studies have shown that they may interrupt various signaling pathways in normal and cancerous skin cells, raising the hypothesis that their use may increase the risk of melanoma skin cancer [4–6].

To date, two observational studies have assessed the association between PDE5-Is and skin cancer [7,8]. Although both studies observed positive associations with melanoma [7,8], the association in one study was limited to those who had filled a single prescription, along with a modest association with basal cell carcinoma (BCC) [8], a cancer in which PDE5 is not thought be involved [9–12].

Given the discrepant findings of the aforementioned studies [7,8] and the widespread use of PDE5-Is, we conducted a large, population-based cohort study to determine whether the use of PDE5-Is is associated with an increased risk of melanoma skin cancer in patients with ED.

2. Patients and methods

2.1. Data source

The study was conducted using the UK Clinical Practice Research Datalink (CPRD). The CPRD contains the medical records of >14 million patients [13] that have been shown to be representative of the UK population [14]. Diagnoses recorded in the CPRD have been shown to have high validity (median positive predictive value of 89%) [14,15]. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 15_118A) and the research ethics board of the Jewish General Hospital (Montreal, Canada).

2.2. Study population

We conducted a cohort study among all men newly diagnosed with ED between January 1, 1998 (the year the first PDE5-I, sildenafil, entered the UK market), and June 30, 2014. The date of the ED diagnosis defined cohort entry. To be included, patients were required to be aged ≥40 yr, to have at least 1 yr of baseline medical history, and to have never been prescribed PDE5-Is at any time before cohort entry (to minimize the inclusion of prevalent users). We also excluded patients diagnosed with any type of skin cancer (melanoma or nonmelanoma skin cancer [BCC, squamous cell carcinoma (SCC), and other nonmelanoma skin cancers] identified using read codes [available on request]) at any time before cohort entry. Finally, all patients were required to have at least 1 yr of follow-up after cohort entry, necessary for latency purposes.

Patients meeting the study inclusion criteria were followed starting 1 yr after cohort entry until an incident diagnosis of skin cancer (melanoma or nonmelanoma skin cancer, the first to occur during follow-up) or censoring on death from any cause, end of registration with the general practice, or end of the study period (June 30, 2015), whichever occurred first.

2.3. Exposure definition

The use of PDE5-Is (sildenafil, tadalafil, and vardenafil) was treated as a time-varying variable in the models. Patients were considered unexposed until the year after the first PDE5-I prescription (ie, after applying a 1-yr lag period) and considered exposed thereafter until the end of follow-up. Lagging the exposure was performed for latency purposes (by imposing a minimum etiological time window between treatment initiation and diagnosis of skin cancer) and to minimize detection bias (ie, when the initiation of a drug is associated with more frequent physician visits and thus a greater probability of diagnosing cancer).

We also considered two secondary time-dependent exposure definitions. In the first, we cumulated the total number of prescriptions received until the time of the event. In the second, we cumulated the total number of pills received up until the time of the event by summing the specified number of pills per prescription through all prescriptions. The reference category for all analyses was nonuse of PDE5-Is up until the time of the event.

2.4. Potential confounders

Along with number of different drug classes and number of physician visits in the year before cohort entry, we adjusted the models for the following potential confounders measured at cohort entry: age, year of cohort entry, alcohol-related disorders, smoking status, body mass index (BMI), and Charlson Comorbidity Index. The models also included known skin cancer risk factors, including the presence of naevi, precancerous skin lesions, use of antiparkinsonian drugs, and immunosuppression (this included medical conditions that require immunosuppressants [rheumatoid arthritis, inflammatory bowel disease, psoriasis, lupus, vasculitis, and previous organ transplant] and use of immunosuppressive and immunomodulatory drugs), all measured at any time before cohort entry. Finally, because users of PDE5-Is may have different health-seeking behaviors than nonusers, we adjusted for influenza vaccination, referral to colonoscopy, and prostate-specific antigen (PSA) testing, all measured in the year before cohort entry, as indicators of health-seeking behavior.

2.5. Statistical analysis

We used descriptive statistics to summarize the characteristics of the entire cohort and of those exposed and unexposed to PDE5-Is at cohort entry. We also calculated crude incidence rates of melanoma and nonmelanoma skin cancer with 95% confidence intervals (CIs) based on the Poisson distribution.

We used time-dependent Cox proportional hazards models to estimate hazard ratios (HRs) with 95% CIs of incident melanoma skin cancer, comparing the use of PDE5-Is with nonuse. For comparison purposes, we conducted identical analyses for BCC and SCC, two nonmelanoma skin cancers that are not thought to involve PDE5 pathways [9–12]. All models were adjusted for the potential confounders listed above.

2.6. Secondary analyses

We conducted three secondary analyses. The first and second assessed whether there was an association in terms of total number of prescriptions and pills received (as described above). These variables were entered in tertile categories in the models, based on their distribution in the cohort. Finally, the third analysis assessed whether the risk varied by type of PDE5-I. For this analysis, the use of PDE5-Is was further categorized into the following four mutually exclusive time-varying exposure categories: sildenafil only, tadalafil only, vardenafil only, and use of more than one type.

2.7. Sensitivity analyses

We conducted seven sensitivity analyses to assess the robustness of our findings, and those are described in detail in Supplement 1 and 2. Briefly,

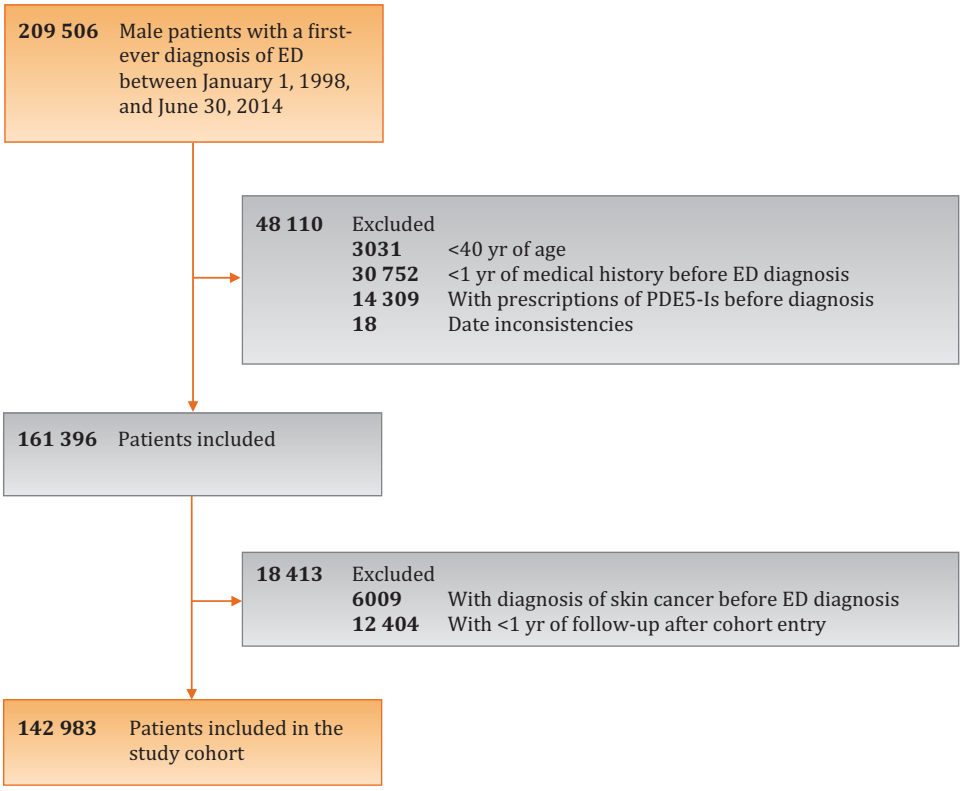

Fig. 1 – Study flow diagram describing the assembly of the erectile dysfunction cohort using the UK Clinical Practice Research Datalink. ED = erectile dysfunction; PDE5-I = phosphodiesterase type 5 inhibitor.

we repeated the analyses using different lag periods, restricted the cohort to patients with health-seeking behaviors, additionally excluded patients with cardiovascular contraindications and prostate cancer, took into account competing risks due to deaths from any cause, and used multiple imputation methods for variables with missing information (BMI and smoking status). Finally, we fitted a marginal structural model to control for potential time-dependent confounding. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

The cohort included 142 983 patients with ED (Fig. 1), for whom the mean age at cohort entry was 59.0 yr (standard deviation [SD] 10.2 yr) and the mean follow-up was 4.9 yr (SD 3.8 yr). Overall, users and nonusers of PDE5-Is were similar for most characteristics, with the exception of PDE5-I users having a lower comorbidity score and fewer physician visits but being more likely to have had an influenza vaccination and a PSA test in the year before cohort entry (Table 1).

The cohort generated 698 479 person-years of follow-up, and 440 patients were newly diagnosed with melanoma skin cancer (crude incidence rate of 63.0 [95% CI, 57.2–69.2] per 100 000 person-years). A total of 3253 and 332 patients were diagnosed with BCC and SCC, generating crude incidence rates of 465.7 (95% CI, 449.9–482.0) and of 47.5 (95% CI, 42.6–52.9) per 100 000 person-years, respectively.

3.1. *Melanoma skin cancer*

The use of PDE5-Is was not associated with a statistically significant increased risk of melanoma skin cancer (66.7 vs 54.1 per 100 000 person-years; adjusted HR: 1.18; 95% CI, 0.95–1.47) (Table 2). In secondary analyses, receiving seven or more prescriptions was associated with a 30% increased risk of melanoma skin cancer (adjusted HR: 1.30; 95% CI, 1.01–1.69). The median number of prescriptions among those who received seven or more prescriptions was 20 (Q1 = 11, Q3 = 39). Similarly, receiving ≥25 pills was associated with 34% increased risk of melanoma skin cancer (adjusted HR: 1.34; 95% CI, 1.04–1.72). No single drug was statistically associated with an increased risk of melanoma skin cancer due to the fewer events in each exposure category, although the HR for sildenafil was elevated (HR: 1.22; 95% CI, 0.97–1.54) (Supplementary Fig. 1).

3.2. *Nonmelanoma skin cancer*

Compared with nonuse, the use of PDE5-Is was not associated with increased risk of BCC or SCC (HR: 1.07 [95% CI, 0.99–1.16] and 1.12 [95% CI, 0.87–1.44], respectively) (Table 3). In secondary analyses, the second tertile categories for number of prescriptions and pills received were significantly associated with an increased risk, although the last tertile categories were not (Table 3).

Table 1 – Baseline characteristics of the cohort overall and according to use of phosphodiesterase type 5 inhibitors at cohort entry

Characteristic	Entire cohort	Phosphodiesterase type 5 inhibitors[†]	
		Use	No use
Number	142 983	58 732	84 611
Age, yr, mean (SD)	59.0 (10.2)	58.8 (9.8)	59.2 (10.4)
Alcohol-related disorders, *n* (%)	18 978 (13.3)	7220 (12.4)	11 758 (13.9)
Smoking status, *n* (%)			
Current	30 007 (21.0)	12 248 (21.0)	17 759 (21.0)
Past	49 650 (34.7)	20 216 (34.6)	29 434 (34.8)
Unknown	4270 (3.0)	1485 (2.6)	2785 (3.3)
Body mass index, kg/m^2, *n* (%)			
<25.0	31 738 (22.2)	13 596 (23.3)	18 142 (21.4)
25–29.9	56 121 (39.3)	23 314 (39.9)	32 807 (38.8)
≥30.0	38 750 (27.1)	14 751 (25.3)	23 999 (28.4)
Unknown	16 374 (11.5)	6711 (11.5)	9663 (11.4)
Precancerous skin lesions, *n* (%)	19 633 (13.7)	8203 (14.1)	11 430 (13.5)
Presence of naevi, *n* (%)	7621 (5.3)	3272 (5.6)	4349 (5.1)
Immunosuppression, *n* (%)	14 959 (10.5)	6335 (10.9)	8624 (10.2)
Antiparkinsonian drugs, *n* (%)	2215 (1.6)	734 (1.3)	1481 (1.8)
Charlson comorbidity score, *n* (%)			
0	72 424 (50.7)	30 035 (51.5)	42 389 (50.1)
1–2	53 199 (37.2)	23 083 (39.5)	30 116 (35.6)
≥3	17 360 (12.1)	5254 (9.0)	12 106 (14.3)
No. of different drug classes, mean (SD)[*]	5.6 (5.2)	5.3 (4.8)	5.7 (5.5)
No. of physician visits, mean (SD)	4.5 (6.8)	4.3 (6.4)	4.6 (7.1)
Health-seeking–related variables[*]			
Influenza vaccination, *n* (%)	43 838 (30.7)	20 396 (34.9)	23 442 (27.7)
Referral to colonoscopy, *n* (%)	1447 (1.0)	604 (1.0)	843 (1.0)
Prostate-specific antigen testing, *n* (%)	17 797 (12.5)	8271 (14.2)	9526 (11.3)

SD = standard deviation.
[*] Measured in the year before cohort entry.
[†] Among patients who received a prescription on the same day as cohort entry (ie, first-ever diagnosis of erectile dysfunction).

Table 2 – Crude and adjusted hazard ratios for the primary and secondary analyses assessing the association between phosphodiesterase type 5 inhibitors and the risk of melanoma skin cancer in a cohort of patients with erectile dysfunction

Phosphodiesterase type 5 inhibitor use	Events	Person-years	Incidence rate (95% CI)[*]	Crude HR	Adjusted HR (95% CI)[†]
Primary analysis					
No use	112	207 001	54.1 (44.6–65.1)	1.00	1.00 [Reference]
Use	328	491 478	66.7 (59.7–74.4)	1.19	1.18 (0.95–1.47)
No. of prescriptions					
1	102	156 051	65.4 (53.3–79.3)	1.20	1.15 (0.88–1.51)
2–6	97	159 915	60.7 (49.2–74.0)	1.09	1.07 (0.82–1.41)
≥7	129	175 512	73.5 (61.4–87.3)	1.28	1.30 (1.01–1.69)
No. of pills					
1–4	90	135 337	66.5 (53.5–81.7)	1.21	1.17 (0.88–1.55)
5–24	89	157 383	56.5 (45.4–69.6)	1.02	1.00 (0.75–1.32)
≥25	149	198 758	75.0 (63.4–88.0)	1.31	1.34 (1.04–1.72)

CI = confidence interval; HR = hazard ratio.
[*] Per 100 000 person-years.
[†] Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used, and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

The use of tadalafil, vardenafil, and use of more than one type of drug were all associated with an increased risk of BCC. These associations were not observed with SCC (Supplementary Fig. 1).

3.3. *Sensitivity analyses*

The results of the sensitivity analyses yielded consistent findings with the exception of two sensitivity analyses (Figure 2 and Supplementary Tables 1–7). Specifically, when restricting the cohort to patients with health-seeking behaviors, the use of PDE5-Is was associated with an increased risk of melanoma skin cancer (HR: 1.46; 95% CI, 1.05–2.04), with evidence of a pattern in terms of prescriptions and pills received (seven or more prescriptions: HR: 1.64 [95% CI, 1.12–2.40]; ≥25 pills: HR: 1.69 [95% CI, 1.16–2.45]) (Supplementary Table 4). Similarly, excluding and censoring patients with cardiovascular contraindications

Table 3 – Crude and adjusted hazard ratios for the primary and secondary analyses assessing the association between phosphodiesterase type 5 inhibitors and the risk of nonmelanoma skin cancer in a cohort of patients with erectile dysfunction

Phosphodiesterase type 5 inhibitor use	Events	Person-years	Incidence rate (95% CI)*	Crude HR	Adjusted HR (95% CI)†
Basal cell carcinoma					
Primary analysis					
No use	900	207 001	434.8 (406.8–464.1)	1.00	1.00 [Reference]
Use	2353	491 478	478.8 (459.6–498.5)	1.05	1.07 (0.99–1.16)
No. of prescriptions					
1	697	156 051	446.6 (414.1–481.1)	1.02	1.01 (0.91–1.11)
2–6	818	159 915	511.5 (477.1–547.8)	1.14	1.15 (1.04–1.26)
≥7	838	175 512	477.5 (445.7–510.9)	1.01	1.06 (0.97–1.17)
No. of pills					
1–4	612	135 337	452.2 (417.1–489.5)	1.03	1.01 (0.91–1.12)
5–24	781	157 383	496.2 (462.0–532.3)	1.11	1.11 (1.01–1.22)
≥25	960	198 758	483.0 (452.9–514.5)	1.03	1.09 (0.99–1.20)
Squamous cell carcinoma					
Primary analysis					
No use	84	207 001	40.6 (32.4–50.2)	1.00	1.00 [Reference]
Use	248	491 478	50.5 (44.4–57.1)	1.12	1.12 (0.87–1.44)
No. of prescriptions					
1	77	156 051	49.3 (38.9–61.7)	1.22	1.12 (0.82–1.54)
2–6	82	159 915	51.3 (40.8–63.6)	1.17	1.17 (0.86–1.59)
≥7	89	175 512	50.7 (40.7–62.4)	1.00	1.07 (0.79–1.46)
No. of pills					
1–4	71	135 337	52.5 (41.0–66.2)	1.30	1.18 (0.86–1.63)
5–24	81	157 383	51.5 (40.9–64.0)	1.18	1.16 (0.85–1.58)
≥25	96	198 758	48.3 (39.1–59.0)	0.97	1.04 (0.77–1.41)

CI = confidence interval; HR = hazard ratio.
* Per 100 000 person-years.
† Adjusted for age, year of cohort entry, alcohol-related disorders, smoking status, body mass index, precancerous skin lesions, presence of naevi, immunosuppression, use of antiparkinsonian drugs, Charlson comorbidity score, number of different drug classes used and number of physician visits in the year before cohort entry, and health-seeking–related variables (influenza vaccination, referral to colonoscopy, and prostate-specific antigen testing, all measured in the year before cohort entry).

led to a higher overall HR for melanoma skin cancer (HR: 1.47; 95% CI, 0.90–2.40), along with evidence of a pattern (seven or more prescriptions: HR: 1.85 [95% CI, 1.05–3.26]; ≥25 pills: HR: 1.84 [95% CI, 1.06–3.18]) (Supplementary Table 5). Finally, the marginal structural model yielded consistent results (marginal HR: 1.11; 95% CI, 0.83–1.47).

4. Discussion

The findings of this large, population-based study indicate that the use of PDE5-Is is not associated with an overall increased risk of melanoma skin cancer; however, in a secondary analysis, the risk was increased with increasing numbers of prescriptions and pills received (30% and 34%, respectively). Overall, these findings remained consistent in several sensitivity analyses.

To our knowledge, two observational studies have been conducted on this subject [7,8]. In the first study, using the Health Professionals Follow-up Study, the use of sildenafil was associated with an 84% increased risk of melanoma skin cancer (HR: 1.84; 95% CI, 1.04–3.22), whereas no association was observed with BCC and SCC [7]; however, exposure was assessed using a questionnaire that was administered at a single time point (in 2000). In the second study, using a nested case-control approach within the Swedish registries, the use of PDE5-Is was associated with an overall increased risk of melanoma (odds ratio [OR]: 1.21; 95% CI, 1.08–1.36), but this association was limited to patients who had filled a single prescription (OR: 1.32; 95% CI, 1.10–1.59) [8]. The authors also reported an association with BCC (HR: 1.19; 95% CI, 1.14–1.25), for which there is no clear biological mechanism for a possible association with PDE5-I use [8].

In contrast to the previous studies [7,8], we restricted our cohort to patients with ED for primarily two reasons. First, comparing PDE5-I users with men from the general population may introduce surveillance bias, as the former have been shown to be more health conscious [8]. This might explain the association with BCC in one of the studies [8]. Second, ED has been shown to be associated with obesity, diabetes, and cardiovascular diseases [16–18], some of which may be directly or indirectly associated with melanoma skin cancer [19]. Consequently, comparing PDE5-I users with nonusers from the general population may introduce confounding by indication.

There is some biological evidence that the use of PDE5-Is may increase the risk of melanoma skin cancer. First, PDE5 is widely expressed in many tissues, including melanocytes [4,20]. Second, it is well established that activating mutations of the oncogene *BRAF* are common in melanoma skin cancer [21]. Although some preclinical studies have raised the possibility that PDE5 inhibition might have therapeutic value in cancer treatment [22,23], Arozarena et al [4] showed that one consequence of *BRAF* activation is suppression of expression of *PDE5A*, the gene that encodes PDE5, and that this leads to increased invasiveness. Consequently, pharmacologic inhibition of PDE5A could simulate the effect of *BRAF* activation on this target gene.

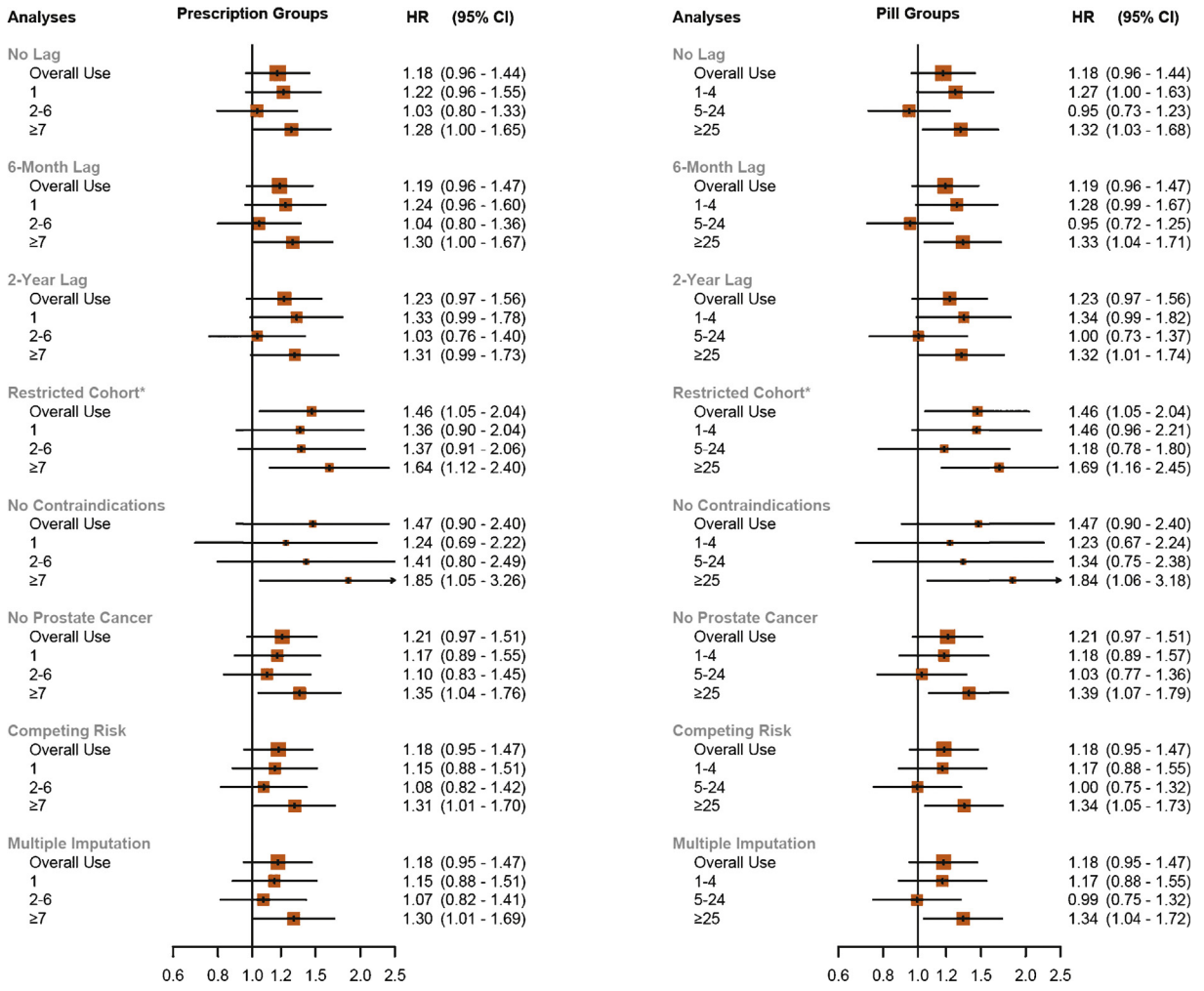

Fig. 2 – Forest plots summarizing the sensitivity analyses for melanoma skin cancer.
CI = confidence interval; HR = hazard ratio.
*** Cohort restricted to patients with at least one health-seeking behavior (influenza vaccination, referral to colonoscopy and prostate-specific antigen testing) in the year before cohort entry.**

This action of PDE5A inhibitors might have little consequence for melanoma cases that already have their target silenced by *BRAF* activation but nevertheless could have a measurable effect based on actions early in melanogenesis and/or on the subset of melanomas that do not have *BRAF* mutations. In addition, a recent study showed that sildenafil promotes melanoma growth by potentiating a cyclic guanosine monophosphate–dependent pathway [6]. Although our primary findings suggest that PDE5-Is are not associated with an overall increased risk of melanoma, our secondary analyses by number of prescriptions and pills are in line with the biological hypothesis of a possible risk; however, these findings need to be replicated in other well-conducted studies.

Our study has a number of strengths. First, restricting the cohort to patients with ED minimized surveillance bias and possible confounding by indication. Second, the use of PDE5-Is was treated as a time-dependent variable in the model, and this eliminated immortal time bias (a bias resulting from misclassifying unexposed person-time as exposed person-time) [24]. Third, we considered exposure lag periods, which were to account for minimum latencies and to minimize detection bias. Finally, we performed a number of sensitivity analyses that produced generally consistent results.

Our study has some limitations. First, the CPRD records prescriptions written by general practitioners and not those filled by patients, leading to some exposure misclassification. Second, although melanoma skin cancer has been shown to be well recorded in the CPRD compared with the UK National Cancer Data Repository [25], it was not possible to assess the association with tumor grade and stage. Finally, it was not possible to adjust the models for ultraviolet radiation, the most important risk factor for melanoma and non-melanoma skin cancer [26,27]; however, confounding would be introduced only if PDE5-I users were more likely to be exposed to ultraviolet radiation than nonusers. To mitigate this issue, we adjusted the models for health-seeking behaviors and performed sensitivity analyses restricting the cohort to such patients as well as excluding patients with

cardiovascular contraindications (the latter being a sicker group less likely to engage in recreational exposure to ultraviolet radiation). We note that the HRs were further elevated in these sensitivity analyses, with a clear pattern in terms of prescriptions and pills received. Furthermore, although our data are consistent with other observational studies reporting a seasonal variation in the diagnosis of melanoma skin cancer (with peaks in the summer months) [28], the prescribing rate of PDE5-Is in our cohort did not follow a seasonal pattern (Supplementary Fig. 2). This argues against the hypothesis that our findings are confounded by some seasonal variation in the prescribing rate of these drugs and the diagnostic rate of melanoma skin cancer. Nonetheless, given the observational nature of the study, residual confounding remains possible and may explain the unexpected pattern observed for BCC and SCC.

5. Conclusions

The findings of this large, population-based study indicate that the use of PDE5-Is is not associated with an overall increased risk of melanoma skin cancer. The modest increased risk observed with seven or more prescriptions and $\geq$25 pills requires further validation.

Author contributions: Laurent Azoulay had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Azoulay, Platt, Suissa.
Acquisition of data: Azoulay.
Analysis and interpretation of data: Lian, Yin, Pollak, Carrier, Platt, Suissa, Azoulay.
Drafting of the manuscript: Lian.
Critical revision of the manuscript for important intellectual content: Lian, Yin, Pollak, Carrier, Platt, Suissa, Azoulay.
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