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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.

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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,

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