Phosphodiesterase Type 5 Inhibitors and Risk of Malignant Melanoma: Matched Cohort Study Using Primary Care Data from the UK Clinical Practice Research Datalink

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Introduction

- Phosphodiesterase type 5 (PDE5) inhibitors are used to treat erectile dysfunction
- Two major epidemiological studies came to differing conclusions on the effect of PDE5 inhibitors on the risk of malignant melanoma:
  - Li et al reported a near doubling of the hazard of melanoma among sildenafil users (HR = 1.84, 95% CI 1.04–3.22)
  - A Swedish study suggested a more modest association between PDE5 inhibitors and melanoma (HR = 1.21, 95% CI 1.08–1.36), but the authors expressed doubts over whether this association was causal
- We aimed to examine the association between PDE5 inhibitors and the risk of incident melanoma in a large cohort of men using data from UK primary care, and to assess the causality of any observed increase in risk

Methods

We carried out a matched cohort study using prospectively collected data from the UK Clinical Practice Research Datalink.

Study Population

- Male patients >18 years
- Incident exposure to PDE5 inhibitor from 1st July 1999 to 1st August 2014 inclusive
- Follow-up began at the date of first PDE5 inhibitor prescription
- Exposed patients were matched to up to four unexposed male controls on age, general practice, and diabetes status

Exposures and Outcome

Primary exposure: ever use of a PDE5 inhibitor

Secondary exposures: cumulative number of PDE5 inhibitor prescriptions (1, 2–4, 5–9, 10–19, 20+), and years since first prescription (0.5, >0.5–1, >1–2, >2–4, >4 years).

Primary outcome: incident malignant melanoma identified by Read codes mapping to ICD-10 code C43.

Control outcomes: basal cell carcinoma, solar keratosis, and colorectal cancer, which are not expected to be associated with PDE5 inhibitor exposure

Statistical Analysis

- The association between exposure variables and melanoma was estimated using a Cox regression with an underlying age timescale, stratified by matched set
- We then adjusted further for a range of potential confounders
- To assess residual confounding by sun exposure, we used conditional logistic regression to estimate the association between prior solar keratosis and starting a PDE5 inhibitor

Results

- 145,104 men aged 18 years with an incident PDE5 inhibitor prescription in the study period were eligible for inclusion
- 135,589 of these men were matched to four controls
- The unadjusted HR showed weak evidence of an increased risk of melanoma in patients exposed to PDE5 inhibitors (HR = 1.16, 95% CI 1.03–1.31)
- There was little change in the estimate when adjusting for all potential confounders (adjusted HR = 1.14, 95% CI 1.01–1.29)
- For basal cell carcinoma and solar keratosis, which are both related to sun exposure, we estimated similar HRs to those observed in the main malignant melanoma analysis
- There was no evidence of any increased risk of colorectal cancer among PDE5 inhibitor users

Conclusions

- We found weak evidence of a small increased risk of melanoma among PDE5 inhibitor users
- But greater exposure did not increase risk
- The association was also not specific to melanoma and was also observed for other sun exposure related conditions
- There was strong evidence that exposed patients were more likely to have had high sun or UV exposure
- These results are not consistent with PDE5 inhibitors being causally associated with melanoma risk, and strongly suggest that observed risk increases are driven by greater sun exposure among patients exposed to a PDE5 inhibitor.