Phosphodiesterase 5 Inhibitor Use and Risk of Conventional and Serrated Precursors of Colorectal Cancer

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ABSTRACT

Background: Phosphodiesterase 5 (PDE5) inhibitors have been hypothesized to have chemoprotective effects in colorectal cancer. Current population-based epidemiologic evidence is, however, limited and inconsistent.

Methods: Among 18,123 men in the Health Professionals Follow-up Study who had at least one lower gastrointestinal endoscopy, we evaluated the association between PDE5 inhibitor use and risk of conventional adenoma and serrated lesion between 2000 and 2010, adjusted for repeated observations and multiple risk factors. We stratified by erectile dysfunction to account for potential "confounding by indication."

Results: We documented 2,595 conventional adenomas and 1,395 serrated lesion polyps during the follow-up period. Using people without erectile dysfunction as reference group, recent PDE5 inhibitor use at baseline was not associated with lower risk of conventional adenoma [erectile dysfunction with PDE5 inhibitors: OR = 1.08; 95% confidence interval (CI) = 0.92–1.26; erectile dysfunction without PDE5 inhibitors: OR = 0.95; 95% CI, 0.85–1.06], serrated lesions (erectile dysfunction with PDE5 inhibitors: OR = 1.19; 95% CI = 0.97–1.45; erectile dysfunction without PDE5 inhibitors: OR = 1.03; 95% CI = 0.89–1.19), or advanced conventional adenomas (erectile dysfunction with PDE5 inhibitors: OR = 1.20; 95% CI = 0.94–1.53; erectile dysfunction without PDE5 inhibitors: OR = 0.95; 95% CI = 0.79–1.14). No association was found for PDE5 inhibitor use ever before as well.

Conclusions: We found no evidence of an association between PDE5 inhibitor use and risk of conventional and serrated precursors of colorectal cancer.

Impact: We show that PDE5 inhibitor use is not associated with precursors of colorectal cancer adjusted for medical and lifestyle risk factors among a large population of men with 10 years of follow-up.

Introduction

Phosphodiesterase 5 inhibitors (PDE5) have been hypothesized to have anticancer activity and have potential in the prevention of colorectal cancer. PDE5 inhibitors inhibited tumorigenesis in mice with reduction of the number of polyps up to 50% (1). Currently, population-based evidence remains lacking. Only three studies were conducted and found conflicting results (2–4), and no study has yet evaluated the association between PDE5 inhibitors and precursors of colorectal cancer.

Methods

We prospectively evaluated the association between PDE5 inhibitors and risk of conventional adenoma and serrated lesion, among 18,123 men in the Health Professionals Follow-up Study (HPFS), who had no diagnosis of polyps or cancer before 2000, had exposure information and have undergone at least one lower gastrointestinal endoscopy during the follow up period between 2000 and 2010. The HPFS is an ongoing prospective cohort of men initiated in 1986 among 51,529 health professionals of age 40–75 years in the United States at baseline. Briefly, participants provided detailed information on demographics and lifestyle every 2 years and diet every 4 years. Endoscopic examinations and diagnosis of colorectal cancer and polyp in the past 2 years were acquired on each biennial questionnaire and validated by medical records. If a participant had more than one endoscopy during the study period, multiple records from the same participant were included in the analysis.

The primary exposure was sildenafil use for erectile dysfunction. In 2000, participants were queried as to whether they had undergone surgery or treatment to correct problems with erections during the past 3 months, including sildenafil, shots or penile injection, vacuum suction, alprostadil, and other treatments, and whether they had ever received any treatment of erectile dysfunction before, including sildenafil. However, no information on the dose or frequency of sildenafil was collected. In the same questionnaire, participants were asked to rate their ability during the past 3 months to have and maintain an erection adequate for intercourse without treatment (very poor, poor, fair, good, or very good). Men with poor or very poor ability were considered to have erectile dysfunction at baseline (5).

We evaluated recent sildenafil use at baseline (in the past 3 months, which was reported in 2000) as the main exposure. As sildenafil was mainly prescribed to treat erectile dysfunction, we stratify the population into three groups by erectile dysfunction status (no erectile dysfunction, erectile dysfunction with PDE5 inhibitors, erectile dysfunction without PDE5 inhibitors) to account for potential "confounding by indication." To account for possible multiple records per participant and handle time-varying

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Table 1. Basic characteristics of study population according to baseline recent sildenafil use and erectile dysfunction, HPFS 2000–2010[a].

Characteristics	No ED ($n = 12,399$)	ED with PDE5 inhibitors ($n = 1,274$)	ED without PDE5 inhibitors ($n = 4,450$)
Person-endoscopies, *n*	28,763	3,018	9,514
Age in y, mean (SD)[a]	66.6 (7.3)	70.6 (7.5)	74.0 (8.0)
White, %	91.3	92.8	91.4
Height in cm, mean (SD)	178.5 (6.8)	179.0 (6.7)	178.9 (6.9)
Body mass index in kg/m^2, mean (SD)	26.0 (3.6)	26.4 (3.7)	27.0 (4.4)
Family history of colorectal cancer, %	15.8	14.7	16.6
Diabetes mellitus, %	7.9	12.8	15.8
Pack-years of smoking, mean (SD)	8.3 (14.2)	11.8 (16.3)	12.1 (17.9)
Alcohol intake in g/d, mean (SD)	11.0 (11.9)	12.7 (13.6)	11.4 (13.5)
Physical activity in MET-h/wk, mean (SD)[b]	34.1 (24.0)	30.9 (21.1)	27.7 (20.1)
Regular aspirin use, %[c]	49.1	53.6	57.1
Total folate intake in μg/d, mean (SD)	640 (230)	643 (237)	620 (227)
Calcium intake in mg/d, mean (SD)	1,000 (338)	1,005 (350)	999 (352)
Vitamin D intake in IU/d, mean (SD)	468 (227)	486 (233)	461 (227)
Processed red meat intake in serving/wk, mean (SD)	1.7 (1.7)	1.9 (1.8)	1.9 (1.9)

Abbreviations: ED, erectile dysfunction; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task; PDE5, phosphodiesterase 5.
[a]All variables are standardized by age except for age itself. Cumulative average values across person-endoscopies are presented. Mean (SD) is presented for continuous variables and number of participants (percentage) for categorical variables.
[b]Physical activity is presented by the product sum of the MET of each specific recreational activity and hours spent on that activity per week.
[c]A standard tablet contains 325 mg aspirin, and regular users were defined as those who used at least 2 standard tablets per week.

covariates, we used an Andersen-Gill data structure with a new record for each 2-year follow-up period during which a participant underwent an endoscopy (6). Men were censored at the diagnosis of any colorectal polyp or colorectal cancer, at the time of death, or end of the follow-up (January 1, 2010), whichever occurred first. Multivariable-adjusted logistic regressions were used for cluster data with generalized estimating equations (GEE) to account for repeated observations and to calculate ORs and 95% confidence interval (CI; ref. 6). We also examined the associations by polyp type (conventional adenomas only, serrated lesions only, or any polyps) and for advanced conventional adenomas (≥10 mm, high-grade dysplasia, or tubulovillous or villous histology).

The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA), and those of participating registries as required.

Table 2. Baseline recent sildenafil use, erectile dysfunction, and risk of conventional adenoma and serrated polyps, HPFS 2000–2010.

	Total person-endoscopies, *n* (%)	Total cases, *n*	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)
Serrated polyps					
No ED	27,308 (70)	965	1 (ref)	1 (ref)	1 (ref)
ED with PDE5 inhibitors	2,856 (7)	120	1.25 (1.02–1.53)	1.19 (0.97–1.46)	1.19 (0.97–1.45)
ED without PDE5 inhibitors	9,059 (23)	310	1.07 (0.93–1.24)	1.03 (0.89–1.20)	1.03 (0.89–1.19)
Conventional adenomas					
No ED	28,138 (70)	1,795	1 (ref)	1 (ref)	1 (ref)
ED with PDE5 inhibitors	2,945 (7)	209	1.11 (0.95–1.30)	1.08 (0.92–1.26)	1.08 (0.92–1.26)
ED without PDE5 inhibitors	9,340 (23)	591	0.97 (0.87–1.09)	0.95 (0.85–1.06)	0.95 (0.85–1.06)
Any polyps					
No ED	28,763 (70)	2,420	1 (ref)	1 (ref)	1 (ref)
ED with PDE5 inhibitors	3,018 (7)	282	1.14 (0.99–1.31)	1.11 (0.97–1.27)	1.11 (0.96–1.27)
ED without PDE5 inhibitors	9,514 (23)	765	0.98 (0.89–1.08)	0.96 (0.87–1.06)	0.95 (0.86–1.05)
Advanced conventional adenomas					
No ED	26,929 (70)	586	1 (ref)	1 (ref)	1 (ref)
ED with PDE5 inhibitors	2,818 (7)	82	1.23 (0.97–1.57)	1.19 (0.93–1.52)	1.20 (0.94–1.53)
ED without PDE5 inhibitors	8,975 (23)	226	0.99 (0.83–1.18)	0.96 (0.80–1.14)	0.95 (0.79–1.14)

Abbreviations: HPFS, Health Professionals Follow-up Study; ED, erectile dysfunction; PDE5, phosphodiesterase 5; OR, odds ratio; CI, confidence interval.
[a]Adjusted for age (continuous variable), race (white or nonwhite), family history (yes or no), height (continuous variable), BMI (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, and ≥30.0 kg/m^2) and time period of endoscopy (in 2-year intervals).
[b]Additionally adjusted for physical activity (<7.5, 7.5–14.9, 15–29.9, 30–59.9, ≥60 MET-hours/week), smoking (never smokers, past smokers with <30 pack-years, past smokers with ≥30 pack-years, current smokers with <30 pack-years, current smokers with ≥30 pack-years), alcohol intake (never, <7, 7–13.9, ≥14 g/d), and regular aspirin use (yes or no).
[c]Additionally adjusted for vitamin D intake (quartiles), calcium intake (quartiles), total folate intake (quartiles), and processed red meat (quartiles).

Results

Among 41,295 person-endoscopies, we documented 1,395 cases of serrated polyps and 2,595 cases of conventional adenomas. Among the three groups, participants who had erectile dysfunction and reported no PDE5 inhibitor use were older and more likely to have diabetes mellitus, smoke, and use aspirin regularly. Participants who had erectile dysfunction and reported using PDE5 inhibitors were more likely to drink alcohol and consume more folate, calcium, and vitamin D (**Table 1**).

Overall, no apparent association was observed between recent sildenafil use at baseline and polyps after adjusting for repeated observations and multiple lifestyle risk factors. Using people without erectile dysfunction as reference group, recent PDE5 inhibitor use at baseline was not associated with lower risk of serrated lesions, conventional adenoma, any polyps or advanced conventional adenomas (**Table 2**). We also evaluated sildenafil use ever before (all recent and prior users) as exposure and no apparent association was found (Supplementary Table S1).

Discussion

PDE5 inhibitors have been proposed as a potential drug for chemoprevention of colorectal cancer. Animal models and gene expression studies suggested its potential role in anticancer activity and prolonged survival. However, population-based studies are limited. Only one study, based on Swedish Hospital Discharge Register, found a significant inverse association between PDE5 inhibitor use and risk of colorectal cancer (adjusted HR, 0.65; 95% CI, 0.49–0.85; ref. 2) among men with benign neoplasms. In the same database, the authors further found that postdiagnostic use of PDE5 inhibitors was associated with decreased risk of colorectal cancer–specific mortality and metastasis (4). Both of the studies, however, had several key limitations. First, data on several key lifestyle risk factors for colorectal cancer, such as smoking and dietary factors, were not available. Second, the low polypectomy rate recorded in the registers raised concerns about other potential uncontrolled confounding

In contrast, we found no evidence of an association between PDE5 inhibitor use and precursors of colorectal cancer after adjusting for main lifestyle risk factors and stratified by erectile dysfunction status. Similarly, a recent case–control study nested in the Health Improvement Network primary care database in the United Kingdom also reported no association between use of PDE5 inhibitors and colorectal cancer among men with erectile dysfunction (3).

The strengths of our study include prospective design with large sample size, long-term follow-up, comprehensive profiling of colorectal cancer risk factors, detailed and repeated data collection, as well as confirmation of polyp diagnosis with detailed recording of histopathologic information based on pathology reports. Because the men are highly educated health professionals, the validity of the self-reported information is high. However, we do not have information on the dose or frequency of sildenafil and only included one type of PDE5 inhibitor. Future population studies with detailed measure of PDE5 inhibitors, comprehensive colorectal cancer risk factors as well as accurate updated outcome diagnosis are warranted to further address the potential preventive role of PDE5 inhibitors in colorectal cancer.

Authors' Disclosures

No disclosures were reported.

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Authors' Contributions

Y. Zhang: Conceptualization, resources, data curation, software, formal analysis, investigation, methodology, writing–original draft, project administration, writing–review and editing. **C.-H. Lo:** Data curation, formal analysis. **E.L. Giovannucci:** Conceptualization, supervision, funding acquisition, validation, methodology, project administration, writing–review and editing.

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