PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLE

Cancer Incidence after Initiation of Antimuscarinic Medications for Overactive Bladder in the United Kingdom: Evidence for Protopathic Bias

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Study Objective To estimate the incidence of 10 common cancers among patients treated with antimuscarinic medications for overactive bladder (AMOABs).

Design Retrospective cohort study.

Data Source United Kingdom's Clinical Practice Research Datalink.

Patients A total of 119,912 adults with no previous cancer diagnosis who were new users of AMOABs —darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium—between January 2004 and December 2012.

Measurements and Main Results Sex-specific incidence rates per 1000 person-years and 95% confidence intervals (CIs) were estimated for each study cancer (bladder, breast, colorectal, lung, melanoma, non-Hodgkin lymphoma, pancreatic, prostate, renal, and uterine cancer) overall and stratified by time since cohort entry and by cumulative AMOAB dose. Among the 119,912 patients followed for 399,365 person-years, 4117 incident study cancers occurred. The incidence rate of prostate cancer was 14.2 (95% CI 12.9–15.5) in the year after cohort entry and decreased markedly thereafter. The incidence rate of bladder cancer was also higher in the year after cohort entry than subsequently (men: 5.5, 95% CI 4.8–6.4; women: 1.2, 95% CI 1.0–1.5). The incidence rates of both prostate and bladder cancer decreased with increasing cumulative dose of AMOAB. We observed no similar relations between incidence rates of other study cancers and time since cohort entry.

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Conflicts of interest: The study was funded by Astellas Pharma Global Development. All authors are employees of RTI Health Solutions (RTI-HS), an independent nonprofit research organization. The contract between RTI-HS and Astellas to conduct this study provides independent publication rights to the research team. The sponsor provided input on the study design but had no role in data collection or analysis. In line with the *Guidance on Good Pharmacovigilance Practices (GVP): Module VIII,* of the European Medicines Agency, the sponsor reviewed the manuscript and provided comments, but the authors made final decisions regarding its content and submission. All authors had full access to all of the data (including statistical reports and tables) and take responsibility for the integrity and accuracy of the data analysis and results.

Partial results from this study were presented at the 31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Boston, Massachusetts, August 22–26, 2015.

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Conclusion High incidence rates of bladder and prostate cancer soon after AMOAB initiation and a negative correlation between incidence and cumulative AMOAB dose suggest that protopathic bias is a more likely explanation for these findings than causality. (Protopathic bias in this context means patients' urinary symptoms prompted treatment with an AMOAB, but the symptoms were actually due to a cancer that was already present, although not yet diagnosed or not yet recorded.) To avoid unnecessary delays in the diagnosis of prostate and bladder cancer, physicians should consider these diseases in patients for whom treatment with AMOABs is indicated.

Key Words cancer, incidence, epidemiology, prostate, bladder, overactive bladder, medications.
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The International Continence Society defines "overactive bladder syndrome" as a condition manifested by urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology.[1] Overactive bladder symptoms adversely affect quality of life.[2] A large majority of patients with overactive bladder symptoms are women, especially among those with urge incontinence.[2, 3] The diagnosis of overactive bladder syndrome should begin with a process to exclude specific disorders that could cause the patient's symptoms, including a careful history, physical examination, and urinalysis for all patients and additional procedures for some.[4] Initial treatment of overactive bladder symptoms may include behavioral therapies and pharmacologic management.[4] Antimuscarinic drugs have been the mainstay of pharmacologic treatment for overactive bladder for several decades. However, improvement in overactive bladder symptoms in patients treated with these drugs is modest,[5] and long-term adherence is generally poor, with less than 10% of patients remaining on treatment after 1 year.[6]

As part of a postapproval commitment to the U.S. Food and Drug Administration (FDA) for mirabegron[7, 8] (a selective β_3-adrenergic agonist), we undertook a study to estimate cancer incidence rates in patients initiating antimuscarinic medications for overactive bladder (AMOABs) in the United Kingdom using the Clinical Practice Research Datalink (CPRD). That study evaluated standard care for overactive bladder (antimuscarinic medications) before creating the group comparator for the subsequent phase of the program, which will compare the safety of mirabegron versus standard care. In the present publication, we report results on the incidence rates of 10 commonly diagnosed cancers, as well as further analyses we conducted to assess the nature of elevated rates observed for prostate and bladder cancer.

Methods

This retrospective cohort study was conducted from January 1, 2004, through December 31, 2012. We used CPRD GOLD data (information from general practitioners' electronic medical records) and, for the subset of general practices in England with linkages, data from Hospital Episode Statistics (HES) and the National Cancer Data Repository (NCDR). The study medications were all the AMOABs available at the time the study was initiated: darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium. Eligible patients were at least 18 years old and had at least 12 months of continuous registration in the database, followed by a first (index) prescription for any of the study medications not prescribed in the preceding 12 months. We excluded patients with a previous diagnosis of cancer (other than nonmelanoma skin cancer) or human immunodeficiency virus (HIV) infection. The study cohort included all eligible patients with data in the CPRD during the study period. Patients were followed from the initiation of the first qualifying AMOAB prescription until the earliest of death, transfer out of their general practice, date of last data collection (practice specific), diagnosis of cancer, evidence of HIV infection (diagnosis of or treatment for HIV), or the end of the study period.

Because the present study was part of an international multidatabase collaboration that includes data sources in the United States, the 10 study cancers selected for evaluation were those with the highest incidence rates in the Surveillance Epidemiology and End Results Reporting database[9]: bladder, breast, colorectal, lung, melanoma, non-Hodgkin lymphoma, pancreatic, prostate, renal, and uterine. Case identification and validation in GOLD data have been described previously.[10] Among the subcohort of the study population with linked data, cases identified in

HES or NCDR data were included in the analysis without further validation.

We estimated crude and age- and sex-standardized incidence rates and their 95% confidence intervals (CIs) for the individual study cancers among new users of any AMOAB. Incidence rates were standardized to the age- and sex-specific person-time contributed by the entire study cohort. Since crude and standardized rates were closely similar to each other, only the standardized incidence rates are reported here unless indicated otherwise. Incidence rates of any study cancer among new users of individual AMOABs were also estimated, stratified by sex. Further analyses stratified the individual cancer incidence rates by time since cohort entry (i.e., time after initiation of the index AMOAB) and by cumulative dose of the individual AMOAB. Study analyses were conducted by using SAS software version 9.3 TS1M2 ([2011] SAS Institute, Inc., Cary, NC) and Stata software version 13.1 ([2014] StataCorp LP, College Station, TX).

The study was designed and implemented in line with the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices*[11]; European Medicines Agency *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII—Postauthorization Safety Studies*[12]; the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance *Guide on Methodological Standards in Pharmacoepidemiology*[13]; and the FDA *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Guidance*[14] and was judged to be exempt from review by the RTI International Institutional Review Board. The protocol was approved by the CPRD Independent Scientific Advisory Committee (protocol number 13_142A) and the U.K. National Cancer Intelligence Network. The study protocol and ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) checklist were registered in the EU PAS Register January 13, 2014, prior to the start of data collection (EU PAS register no. ENCEPP/SDPP/5529).

Results

Of 173,927 users of AMOABs in the CPRD initial data set, 54,015 patients were excluded for the following reasons: 37,108 for not having a study drug prescription that qualified as an index prescription, 16,860 for a cancer diagnosis on or before the cohort entry date, 38 for HIV infection/acquired immunodeficiency syndrome (AIDS) on or before the cohort entry date, 8 for both cancer and HIV infection/AIDS on or before the cohort entry date, and 1 because the patient identification number was reported by the general practitioner (GP) to represent a "test patient" created for training purposes. Thus, a total of 119,912 eligible new users of the study AMOABs were identified, of whom 61,993 (51.7%) had data linkable to the HES and/or NCDR databases. Characteristics of the patients at cohort entry (overall and stratified by age, < 65 vs ≥ 65 yrs) are shown in Table 1. Nearly half the patients were aged 65 years or older, and almost 70% were female. Calendar years of cohort entry were well distributed throughout the study period. About half the patients had a recorded Read code diagnosis of overactive bladder or related symptoms (Read codes are provided in Table S1). Other characteristics and comorbidities are listed in Table 1.

The AMOABs commonly used at cohort entry were oxybutynin (40,651 patients [33.9%]), tolterodine (37,506 patients [31.3%]), and solifenacin (33,120 patients [27.6%]). Fewer patients initiated trospium (6071 [5.1%]) or fesoterodine (2344 [2.0%]), and new use of darifenacin was negligible (151 patients [0.1%]). The mean $\pm$ SD duration of the first episode of use of AMOAB ranged from 5.5 ± 10.9 months for oxybutynin to 8.9 ± 14.4 months for darifenacin. During follow-up, 73% of patients were exposed to only a single study AMOAB.[15]

Altogether, 4117 incident study cancers were identified during 399,365 person-years of follow-up: 932 prostate, 886 female breast, 545 colorectal, 534 bladder, 495 lung, 182 melanoma, 144 non-Hodgkin lymphoma, 138 pancreatic, 136 uterine, and 125 renal. The incidences of any study cancer in relation to treatment with each individual AMOAB, stratified by sex, are shown in Table S2. There was no substantial variation in the incidence rates of the study cancers in relation to the individual AMOABs.

Cancer incidence rates in relation to exposure to any AMOAB, stratified by sex, are presented in Table 2. (All incidence rates and CIs herein are reported per 1000 person-yrs.) For cancers that occur in both men and women, the rates were consistently higher in men except for melanoma. Prostate cancer accounted for nearly half of the study cancers identified among men (932 of 1917 events). The incidence rate of prostate cancer was 8.2 (95% CI 7.7–8.8). Bladder cancer represented approximately one-third of study

Table 1. Characteristics of Patients Exposed to Any Overactive Bladder Drug at Study Cohort Entry, Overall and Stratified by Age at Cohort Entry

Characteristic	Age at Cohort Entry[a] < 65 Yrs (n=61,595) No. of Patients (%)	Age at Cohort Entry[a] ≥ 65 Yrs (n=58,317) No. of Patients (%)	Overall (n=119,912) No. of Patients (%)
Age at cohort entry (yrs)			
Mean (SD)	49.1 (11.2)	76.5 (7.5)	62.4 (16.7)
18–24	2217 (3.6)		2217 (1.8)
25–34	5011 (8.1)		5011 (4.2)
35–44	12,005 (19.5)		12,005 (10.0)
45–54	18,411 (29.9)		18,411 (15.4)
55–64	23,951 (38.9)		23,951 (20.0)
65–74		25,429 (43.6)	25,429 (21.2)
75–84		23,612 (40.5)	23,612 (19.7)
≥ 85		9276 (15.9)	9276 (7.7)
Sex			
Male	16,160 (26.2)	20,019 (34.3)	36,179 (30.2)
Female	45,435 (73.8)	38,298 (65.7)	83,733 (69.8)
Calendar year at cohort entry			
2004	6304 (10.2)	6294 (10.8)	12,598 (10.5)
2005	6311 (10.2)	6375 (10.9)	12,686 (10.6)
2006	5980 (9.7)	6231 (10.7)	12,211 (10.2)
2007	6356 (10.3)	6078 (10.4)	12,434 (10.4)
2008	6363 (10.3)	5918 (10.1)	12,281 (10.2)
2009	6988 (11.3)	6405 (11.0)	13,393 (11.2)
2010	7235 (11.7)	6635 (11.4)	13,870 (11.6)
2011	7858 (12.8)	7140 (12.2)	14,998 (12.5)
2012	8200 (13.3)	7241 (12.4)	15,441 (12.9)
Index of multiple deprivation[b]			
1	12,661 (20.6)	14,092 (24.2)	26,753 (22.3)
2	11,737 (19.1)	12,839 (22.0)	24,576 (20.5)
3	12,152 (19.7)	11,970 (20.5)	24,122 (20.1)
4	13,294 (21.6)	11,017 (18.9)	24,311 (20.3)
5	11,751 (19.1)	8399 (14.4)	20,150 (16.8)
Overactive bladder	32,604 (52.9)	26,898 (46.1)	59,502 (49.6)
Hypertension			
Diagnosis codes only	18,762 (30.5)	16,183 (27.8)	34,945 (29.1)
Medications only	4214 (6.8)	819 (1.4)	5033 (4.2)
Diagnosis codes and medications	18,186 (29.5)	38,574 (66.1)	56,760 (47.3)
Diabetes mellitus			
Diagnosis codes only	741 (1.2)	2044 (3.5)	2785 (2.3)
Medications only	279 (0.5)	63 (0.1)	342 (0.3)
Diagnosis codes and medications	3349 (5.4)	7019 (12.0)	10,368 (8.6)
Smoking			
Never	29,328 (47.6)	27,460 (47.1)	56,788 (47.4)
Former	17,137 (27.8)	25,092 (43.0)	42,229 (35.2)
Current	14,386 (23.4)	5065 (8.7)	19,451 (16.2)
Unknown history	744 (1.2)	700 (1.2)	1444 (1.2)
Alcohol use			
Nondrinker	7983 (13.0)	8306 (14.2)	16,289 (13.6)
Low to moderate intake	31,530 (51.2)	30,909 (53.0)	62,439 (52.1)
High to very high intake	11,493 (18.7)	10,515 (18.0)	22,008 (18.4)
Drinker unknown quantity	3579 (5.8)	3537 (6.1)	7116 (5.9)
Unknown history	7010 (11.4)	5050 (8.7)	12,060 (10.1)
Alcohol-related conditions			
Alcoholism or alcohol-related diseases	2357 (3.8)	1149 (2.0)	3506 (2.9)
No alcoholism or alcohol-related diseases	59,238 (96.2)	57,168 (98.0)	116,406 (97.1)
History of acute myocardial infarction	782 (1.3)	4028 (6.9)	4810 (4.0)
History of stroke	1618 (2.6)	6691 (11.5)	8309 (6.9)
History of transient ischemic attack	627 (1.0)	4241 (7.3)	4868 (4.1)
History of coronary heart disease	2712 (4.4)	12,829 (22.0)	15,541 (13.0)
History of heart failure	301 (0.5)	3568 (6.1)	3869 (3.2)

(continued)

Table 1. (continued)

Characteristic	Age at Cohort Entry[a] < 65 Yrs (n=61,595) No. of Patients (%)	Age at Cohort Entry[a] ≥ 65 Yrs (n=58,317) No. of Patients (%)	Overall (n=119,912) No. of Patients (%)
History of peripheral artery disease/ peripheral vascular disease	2359 (3.8)	6033 (10.3)	8392 (7.0)
Menopause (females only)	12,307 (27.1)	7532 (19.7)	19,839 (23.7)
Health services utilization, mean (SD)			
Outpatient visits	9.5 (8.6)	12.2 (10.0)	10.8 (9.4)
Hospitalizations	0.5 (1.3)	0.6 (1.2)	0.5 (1.3)

[a]Study cohort entry is date of index prescription.
[b]Index of multiple deprivation is an area-based measure of relative deprivation used as a proxy for socioeconomic data (which are generally poorly recorded in primary care data since they do not relate directly to a patient's care). Data are provided as quintiles, with quintile 1 representing the most deprived areas and quintile 5 representing the least deprived areas.

cancers other than prostate cancer among men (325 of 985 non–prostate cancer events). The incidence rate of bladder cancer in men was 2.9 (95% CI 2.6–3.2) and in women was 0.7 (95% CI 0.6–0.8).

Select cancer incidence rates by sex and stratified by time since cohort entry (i.e., years after start of the index AMOAB) are shown in Figures 1 and 2 (stratified in 6-mo intervals for 5 yrs after cohort entry) and Table S3 (stratified in 1-yr intervals for all available follow-up). The prostate cancer incidence rate was 14.2 (95% CI 12.9–15.5) for the period up to 1 year since cohort entry and 6.8 (95% CI 5.8–7.9) for the second year after entry; then the rate decreased more gradually thereafter. The bladder cancer incidence rate was similarly greater soon after cohort entry than later: among men, 5.5 (95% CI 4.8–6.4) up to 1 year since cohort entry, 2.5 (95% CI 1.9–3.2) for the second year since entry, and lower for most subsequent years; among women, 1.2 (95% CI 1.0–1.5) up to 1 year since entry, and ranged from 0.3 to 0.7 for all subsequent years. Stratified by 6-month intervals, the incidence rate of prostate cancer in the first 6 months after cohort entry was 19.3 (95% CI 17.3–21.6), and the rates for subsequent 6-month periods were all lower. Other commonly occurring study cancers (i.e., those with the most precise rate estimates) did not show this pattern of rapidly decreasing incidence rates over time since cohort entry (Figures 1 and 2).

There were no meaningful changes in the observed patterns when we carried out similar analyses further stratifying the incidence rates by calendar year of each patient's cohort entry (2004–2006, 2007–2009, and 2010–2012; data not shown).

Cancer incidence rates were also estimated in relation to cumulative exposure to each study medication; results for bladder cancer and prostate cancer among users of the most frequently prescribed AMOABs are presented in Table 3. In general, there was no trend of increasing cancer incidence by cumulative exposure; to the contrary, cancer incidence rates tended to decrease with increasing cumulative dose of the study medications.

We also estimated incidence rates of prostate and bladder cancer according to whether patients had a diagnosis of overactive bladder syndrome or related symptoms recorded (Read codes used to identify diagnoses are provided in Table S1). The rationale for this analysis was that physicians might be more likely to record a diagnosis of overactive bladder syndrome or related symptoms for patients they consider to have unexplained urinary complaints than for patients in whom a prostate or bladder cancer is suspected but not yet diagnosed. Altogether, 49.6% of patients had a diagnosis of overactive bladder syndrome or related symptoms recorded at cohort entry. Consistent with this rationale, incidence rates for prostate and bladder cancer were both found to be substantially lower among patients with a recorded history of overactive bladder syndrome or related symptoms than for those without such. For example, among patients entering the cohort in 2004–2006, the prostate cancer incidence rate was 5.4 (95% CI 4.5–6.4) among those with a prior overactive bladder diagnosis or symptoms recorded and 8.4 (95% CI 7.5–9.5) among those without this information. However, in both subgroups, a similar pattern of decreasing incidence during the first and second years after cohort entry was observed; among those with a prior overactive bladder diagnosis or symptoms, the prostate cancer incidence rate was 8.9 (95% CI 6.3–12.1) for 0–1 year after entry and 4.2 (95% CI 2.4–6.7) for the second year after entry, whereas among those with no

Table 2. Cancer Incidence Rates for Patients Exposed to Any Overactive Bladder Drug, by Cancer Type and Sex

Cancer Type	No. of Events	Individuals Contributing Person-Time	Person-Time (Yrs)	Incidence Rate (per 1000 Person-Years)[a]	95% CI
Bladder cancer					
Men	325	36,157	113,294	2.87	2.57–3.20
Women	209	83,702	286,071	0.73	0.63–0.84
Breast cancer (women)[b]	886	83,681	286,005	3.10	2.90–3.31
Colorectal cancer					
Men	233	36,157	113,294	2.06	1.80–2.34
Women	312	83,702	286,071	1.09	0.97–1.22
Lung cancer					
Men	214	36,157	113,294	1.89	1.64–2.16
Women	281	83,702	286,071	0.98	0.87–1.10
Melanoma					
Men	49	36,157	113,294	0.43	0.32–0.57
Women	133	83,702	286,071	0.46	0.39–0.55
Non-Hodgkin lymphoma					
Men	63	36,157	113,294	0.56	0.43–0.71
Women	81	83,702	286,071	0.28	0.22–0.35
Pancreatic cancer					
Men	48	36,157	113,294	0.42	0.31–0.56
Women	90	83,702	286,071	0.31	0.25–0.39
Prostate cancer (men)	932	36,157	113,294	8.23	7.71–8.77
Renal cancer					
Men	53	36,157	113,294	0.47	0.35–0.61
Women	72	83,702	286,071	0.25	0.20–0.32
Uterine cancer (women)[c]	136	62,163	203,953	0.71	0.60–0.84

CI = confidence interval.
[a]Incidence rates are standardized to the age–sex distribution of the full study cohort.
[b]Follow-up time for breast cancer incidence rate was censored after a bilateral mastectomy. Also, women with a history of bilateral mastectomy at study entry were omitted.
[c]Follow-up time for uterine cancer incidence rate was censored after a hysterectomy. Also, women with a history of hysterectomy at study entry were omitted.

prior overactive bladder diagnosis or symptoms recorded, the corresponding rates were 19.2 (95% CI 15.8–23.0) and 6.4 (95% CI 4.4–9.0). These patterns were similar for all calendar periods of cohort entry, for each individual AMOAB, and for both bladder and prostate cancer (data not shown).

Discussion

We observed transiently high incidence rates of bladder and prostate cancer soon after initiation of medical treatment for overactive bladder symptoms, but the incidence of other common types of cancers did not show this pattern. The elevated bladder and prostate cancer incidence rates occurred so soon after initiation of AMOAB therapy that a causal effect of such treatment was unlikely. Moreover, the observed negative correlation between the incidence of these cancers and cumulative dose of the study AMOAB would represent an unusual pattern for a cancer-causing exposure since the risk of cancer with many known carcinogens increases with cumulative exposure.

A more likely explanation for these findings is protopathic bias—that is, patients' urinary symptoms prompted treatment with an AMOAB, but the symptoms were actually due to a cancer that was already present, although not yet diagnosed or not yet recorded. Since GPs may have been less likely to record an overactive bladder diagnosis or symptoms for a patient in whom they suspected an underlying cancer (than for a patient in whom no cancer was suspected), the higher incidence rates of bladder and prostate cancer in patients without overactive bladder diagnoses or recorded symptoms (compared with those having such diagnoses or symptoms in their record) provides further support for this explanation. Still, we observed a decrease in the incidence of bladder and prostate cancer after the first year of follow-up in those with and those without a diagnosis of overactive bladder or related symptoms, suggesting that protopathic bias was likely a factor even in the latter subgroup.

Although surgical, medical, and radiation therapy of bladder and prostate cancers can result in bladder irritability that may sometimes be treated with overactive bladder medications,[16–18] we

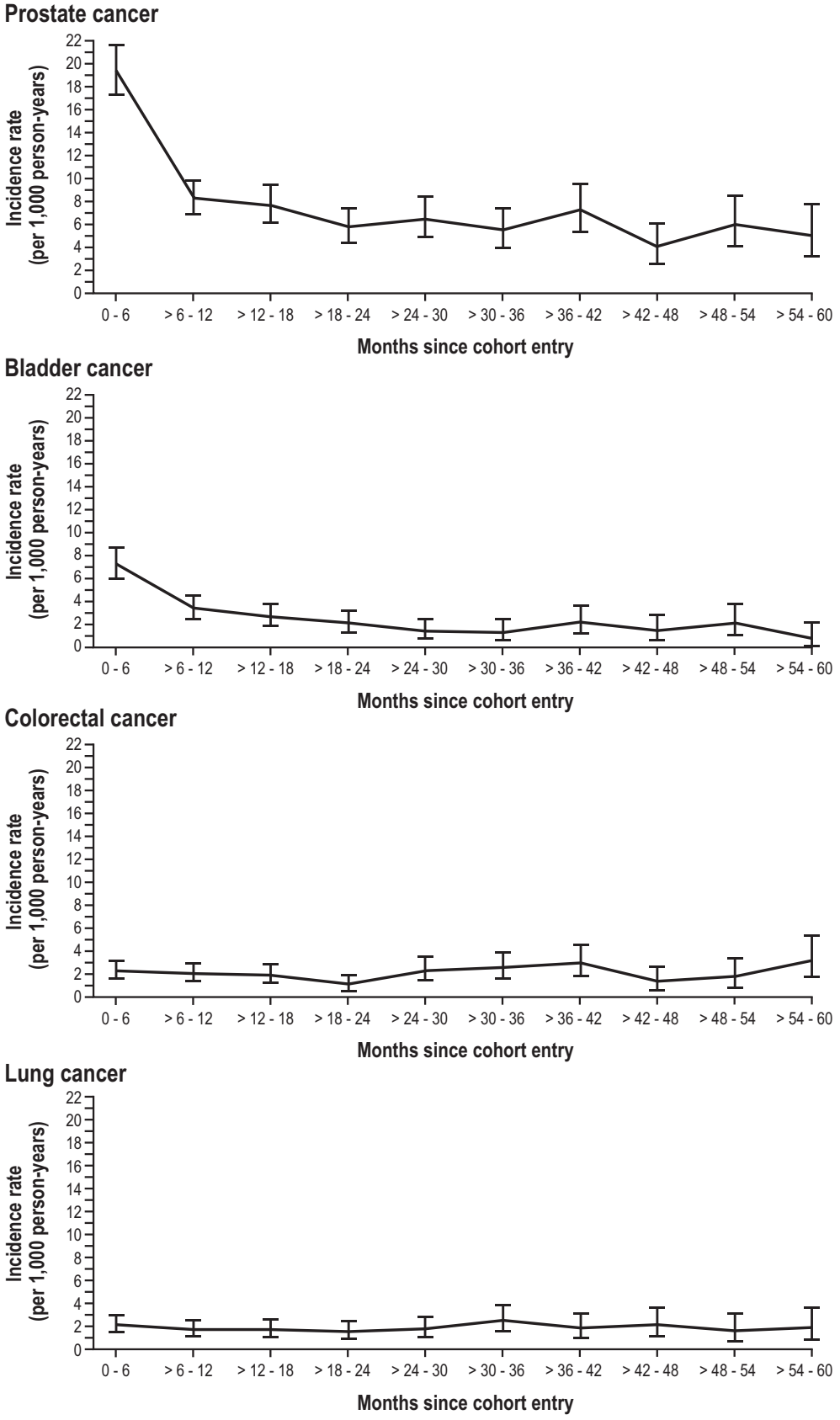

Figure 1. Cancer rates by time since cohort entry in men. Incidence rates were standardized to the age-sex distribution of the full study cohort. Vertical bars represent 95% confidence intervals.

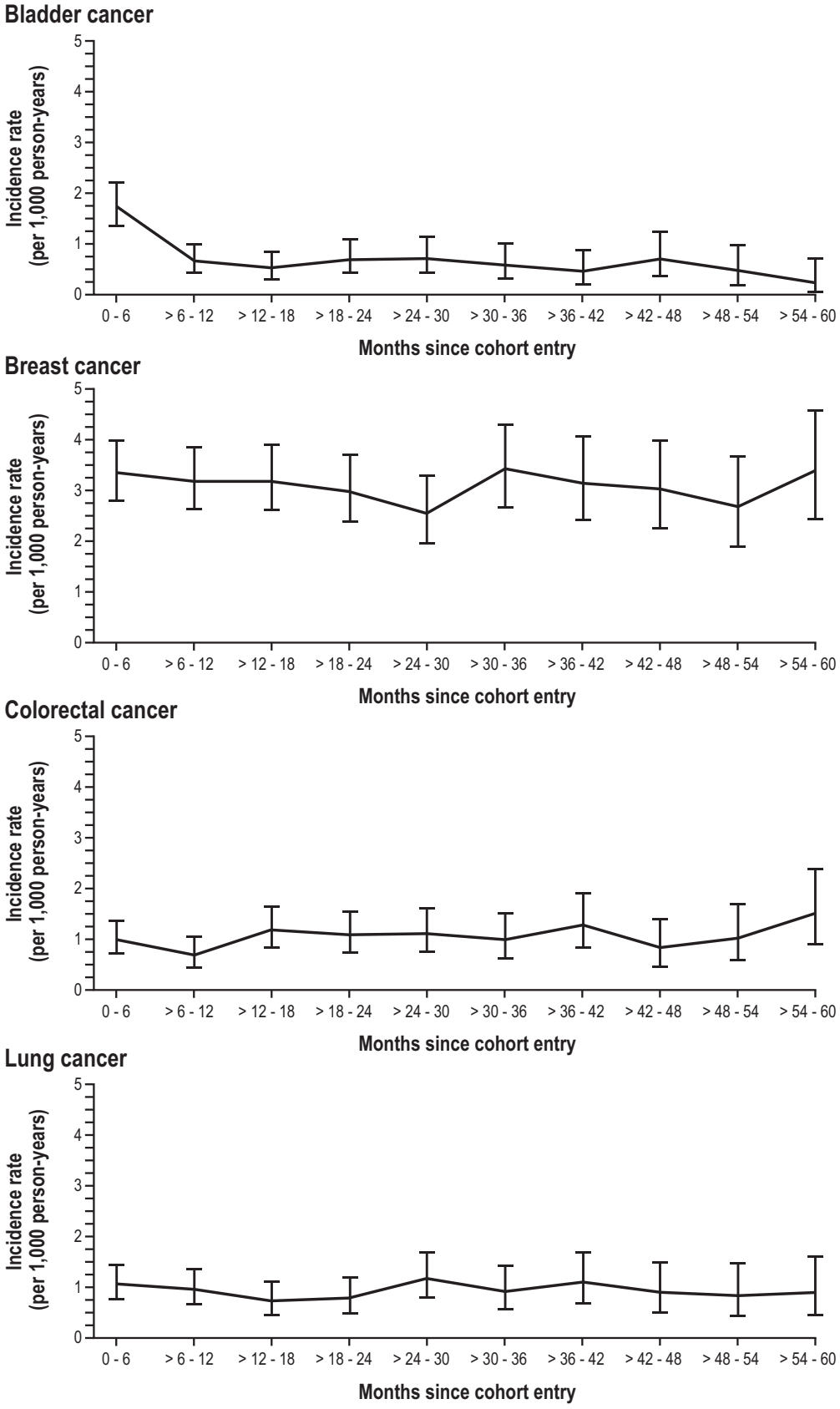

Figure 2. Cancer rates by time since cohort entry in women. Incidence rates were standardized to the age-sex distribution of the full study cohort. Vertical bars represent 95% confidence intervals.

Table 3. Bladder and Prostate Cancer Incidence Rates for Patients Exposed to the Most Frequently Prescribed Overactive Bladder Medication, by Cumulative Dose

Cancer, OAB Medication, Cumulative Dose Category (mg)	No. of Events	No. of Individuals Contributing Person-Time	Person-Time (Yrs)	Incidence Rate (per 1000 Person-Years)[a]	95% CI
Bladder cancer, men					
Oxybutynin					
≤ 200	70	15,369	16,464	4.34	3.38–5.48
200–1000	58	9887	17,592	3.41	2.59–4.41
> 1000	22	4004	10,863	1.94	1.22–2.95
Tolterodine					
≤ 200	57	14,076	21,602	2.77	2.10–3.60
200–1300	57	8589	21,275	2.66	2.02–3.45
> 1300	27	3270	10,976	2.05	1.35–2.99
Solifenacin					
≤ 200	28	12,438	8217	3.56	2.36–5.14
200–1800	49	9054	13,770	3.55	2.62–4.69
> 1800	17	3544	7594	2.02	1.17–3.24
Bladder cancer, women					
Oxybutynin					
≤ 200	47	34,278	44,358	1.03	0.76–1.37
200–1000	35	20,777	39,252	0.88	0.61–1.22
> 1000	14	8282	23,885	0.51	0.28–0.87
Tolterodine					
≤ 200	44	32,298	58,052	0.77	0.56–1.03
200–1300	26	19,047	52,218	0.51	0.34–0.75
> 1300	17	7234	25,726	0.54	0.31–0.86
Solifenacin					
≤ 200	31	35,946	29,964	1.14	0.77–1.62
200–1800	30	25,193	42,759	0.77	0.52–1.10
> 1800	18	10,022	23,238	0.71	0.42–1.13
Prostate cancer					
Oxybutynin					
≤ 200	176	15,369	16,464	11.02	9.45–12.78
200–1000	148	9887	17,592	8.68	7.33–10.19
> 1000	67	4004	10,863	5.89	4.56–7.49
Tolterodine					
≤ 200	172	14,076	21,602	8.34	7.14–9.68
200–1300	155	8589	21,275	7.19	6.10–8.42
> 1300	69	3270	10,976	5.38	4.18–6.82
Solifenacin					
≤ 200	97	12,438	8217	12.24	9.93–14.94
200–1800	110	9054	13,770	7.95	6.53–9.58
> 1800	42	3544	7594	5.01	3.60–6.78

CI = confidence interval; OAB = overactive bladder.
[a]Incidence rates are standardized to the age–sex distribution of the full study cohort.

consider it unlikely that the patterns of incidence rates reported in the present study were due to known cancer diagnoses. Treatment of prostate and bladder cancers may be initiated by specialists, but a GP not recording a known cancer diagnosis when a complication of its treatment has prompted the prescription of a new medication would represent a questionable quality of medical care.

A possible limitation of our analysis is that we did not investigate whether there was variation by age in the increased incidence rates of prostate and bladder cancer soon after cohort entry. Further evaluation of this question may be informative when similar studies are conducted in the future.

The results of this study are consistent with concerns expressed elsewhere. Current treatment guidelines for overactive bladder syndrome advise that the clinician should engage in a diagnostic process to document symptoms and signs that characterize overactive bladder and exclude other disorders that could be the cause of the patient's symptoms.[4] Moreover, in Consumer Health Information recently published by the FDA, it was noted that "some conditions—such as . . . prostate disease and bladder tumors—have symptoms similar to overactive bladder and should be excluded

before a proper diagnosis [of overactive bladder syndrome] can be made."[19]

The CPRD is an excellent data resource for conducting studies such as this. Prescriptions written by GPs are recorded at the time they are provided to patients; although this does not guarantee that prescriptions were filled or that medications were actually taken, the automated system provides a full record of medications prescribed by GPs. Moreover, the diagnosis of many cancer types has been well validated in the CPRD, although it has become apparent recently that using linked data sources increases the number of cancers identified beyond those documented in GP records alone.[20, 21] In a validation substudy, we confirmed the high reliability of cancer diagnoses in the present study population.[10] Finally, although cancer diagnoses are sometimes recorded in GP records later than when the diagnosis was actually established,[22] we doubt that this more general issue is sufficient to account for the findings presented here because the elevated rates we observed soon after cohort entry were limited to prostate and bladder cancers.

To our knowledge, this is the first study that quantitatively estimates the risk of common cancers among users of AMOABs.[23] Two other studies (also components of the same international, multidatabase collaboration), which used the Danish and Swedish National Registers and the same common protocol as our study, subsequently obtained information on prostate and bladder cancer incidence rates stratified by time since cohort entry that are closely similar to those presented here.[24, 25]

Conclusion

Our findings of high incidence rates of bladder and prostate cancer soon after AMOAB initiation and a negative correlation between incidence and cumulative AMOAB dose suggest that protopathic bias is a more likely explanation for these findings than causality. As noted in treatment guidelines cited previously,[4] physicians who prescribe overactive bladder medications should be aware of the possibility that patients with overactive bladder symptoms may have an undiagnosed bladder or prostate cancer. Diagnostic testing to evaluate patients for the presence of these malignancies should be considered when overactive bladder medications are initiated if it is possible that an undiagnosed malignancy is already present.

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Supporting Information

The following supporting information is available in the online version of this paper:

Table S1. Read codes for overactive bladder syndrome and related symptoms or procedures.

Table S2. Incidence rates of any study cancer in relation to treatment with antimuscarinic medications for overactive bladder, stratified by sex.

Table S3. Cancer incidence rates stratified by time since cohort entry, by sex.