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. Overactive bladder symptoms adversely affect quality of life. A large majority of patients with overactive bladder symptoms are women, especially among those with urge incontinence. 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. Initial treatment of overactive bladder symptoms may include behavioral therapies and pharmacologic management. 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, and long-term adherence is generally poor, with less than 10% of patients remaining on treatment after 1 year.

As part of a postapproval commitment to the U.S. Food and Drug Administration (FDA) for mirabegron (a selective β3-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: bladder, breast, colorectal, lung, melanoma, non-Hodgkin lymphoma, pancreatic, prostate, renal, and uterine. Case identification and validation in GOLD data have been described previously. 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 Practices11; the European Medicines Agency Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII—Postauthorization Safety Studies12; the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology13; and the FDA Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Guidance14 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 (33,120 patients [27.6%]), and new use of darifenacin was negligible (151 patients [0.1%]). The mean ± 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<sup>a</sup> |            |            | Overall (n=119,912) |
|-----------------------------------------------|---------------------------------|------------|------------|-------------------|
|                                               | No. of Patients (%)             | < 65 Yrs (n=61,595) | ≥ 65 Yrs (n=58,317) | 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) | 13,399 (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<sup>b</sup>     |                                 |            |            |                  |
| 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)                   | 38,374 (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)                      | 3337 (5.6) | 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) | 4688 (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)
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

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**Table 1.** (continued)

| Characteristic                                      | Age at Cohort Entry<sup>a</sup> | Overall (n=119,912) |
|-----------------------------------------------------|---------------------------------|--------------------|
|                                                     | No. of Patients (%)             | No. of Patients (%) | No. of Patients (%) |
| History of peripheral artery disease/peripheral vascular disease | 239 (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)          |

<sup>a</sup>Study cohort entry is date of index prescription.

<sup>b</sup>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.
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, we

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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) | 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)    | 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)   | 136          | 62,163                               | 203,933           | 0.71                                   | 0.60–0.84 |

CI = confidence interval.

*aIncidence rates are standardized to the age–sex distribution of the full study cohort.

*bFollow-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.

*cFollow-up time for uterine cancer incidence rate was censored after a hysterectomy. Also, women with a history of hysterectomy at study entry were omitted.
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.
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. 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.

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. In a validation study, we confirmed the high reliability of cancer diagnoses in the present study population. Finally, although cancer diagnoses are sometimes recorded in GP records later than when the diagnosis was actually established, 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. 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.

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, 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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References

1. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;1:4–20.
2. Marinovic SP, Rovner ES, Moldwin RM, Stanton SL, Gillen LM, Marinovic CM. The management of overactive bladder syndrome. BMJ 2012;344:e2365.
3. Nygaard I. Clinical practice. Idiopathic urgency urinary incontinence. N Engl J Med 2010;12:1136–62.
4. Gormley E, Lightner D, Burgio K, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline 2014. Available from https://www.auanet.org/commong/pdf/education/clinical-guidance/Overactive-Bladder.pdf. Accessed November 6, 2015.
5. Reynolds WS, McPeeters M, Blume J, et al. Comparative effectiveness of anticholinergic therapy for overactive bladder in women: a systematic review and meta-analysis. Obstet Gynecol 2015;6:1423–32.
6. Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. J Urol 2014;4:1003–8.
7. Food and Drug Administration. NDA approval letter for Myrbetriq (mirabegron) 25 mg and 50 mg extended release tablets. NDA 202611, 28 June 2012. Available from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202611Orig1s000lr/pdf. Accessed August 18, 2015.
8. Food and Drug Administration. Approval package for application number 202611Orig1s000. June 28, 2012. Available from http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202611Orig1s000Approv.pdf. Accessed April 20, 2017.
9. SEER: SEER Cancer Statistics Review 1975–2009 (vintage 2009 populations). Table 1.1. Age-adjusted SEER incidence and US death rates and 5-year relative survival (percent) by primary cancer site, sex, and time period, 2012. Available from http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php. Accessed August 8, 2012.
10. Fortuny J, Kaye JA, Margulis A, et al. Validity of cancer diagnoses in general practitioner medical records (poster presentation). Abstract #899 in Abstracts of the 31st International Conference on Pharmacoepidemiology and Therapeutic Risk
OVERACTIVE BLADDER DRUGS AND CANCER INCIDENCE Kaye et al

11. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 2), 25 Apr 2013. Available from http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed August 18, 2015.

12. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (EMA/95098/2010, 2015. Available from http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific_guideline/2011 Rev 2), 25 Apr 2013. Available from http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed August 18, 2015.

13. ENCePP. Guide on methodological standards in pharmacoepidemiology (revision 4). EMA/95098/2010, 2015. Available from http://www.encepp.eu/standards_and_guidances/methodological_guide.shtml. Accessed July 22, 2015.

14. Food and Drug Administration. Guidance for industry and FDA staff. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data, May 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243337.pdf. Accessed August 18, 2015.

15. Margulis A, McQuay L, Perez-Gutthann S, Kaye JA, Arana A. Use of overactive bladder medications in the adult population of the UK: a cohort study in the Clinical Practice Research Datalink (poster presentation). Abstract #215 in Abstracts of the 31st International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 22–26, 2015, Boston, MA. Pharmacoepidemiol Drug Saf 2015;24:1–587.

16. Boettcher M, Haselhuhn A, Jakse G, Brehmer B, Kirschner-Hermanns R. Overactive bladder syndrome: an underestimated long-term problem after treatment of patients with localized prostate cancer? BJU Int 2012;12:1824–30.

17. Johnson MH, Nepple KG, Peck V, et al. Randomized controlled trial of oxybutynin extended release versus placebo for urinary symptoms during intravesical Bacillus Calmette-Guerin treatment. J Urol 2013;189:4:1268–74.

18. Zhang Z, Cao Z, Xu C, et al. Solifenacin is able to improve the irritative symptoms after transurethral resection of bladder tumors. Urology 2014;1:117–21.

19. Food and Drug Administration. Need relief from overactive bladder symptoms? July 2015. Available from http://www.fda.gov/forconsumers/consumerupdates/ucm426090.htm. Accessed April 20, 2017.

20. Dregan A, Moller H, Murray-Thomas T, Guilliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. Cancer Epidemiol 2012;3:425–9.

21. Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. Pharmacoepidemiol Drug Saf 2013;2:168–75.

22. Walker AM. Identification of esophageal cancer in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2011;11:1139–67.

23. Kaye JA, Margulis A, Plana E, Calingaert B, Perez-Gutthann S, Arana A. Cancer rates over time after initiation of overactive bladder drugs (oral presentation). Abstract #52 in Abstracts of the 31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 22–26, 2015, Boston, MA. Pharmacoepidemiol Drug Saf 2015;24:1–587.

24. Hallas J, Margulis A, Pottegard A, et al. Elevated bladder and prostate cancer rates following initiation of OAB medication: Findings from a Danish Registry (poster presentation). Abstract #918 in Abstracts of the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, The Convention Centre Dublin, Dublin, Ireland, August 25–28, 2016. Pharmacoepidemiol Drug Saf 2016;25:3–679.

25. Linder M, Margulis A, Anveden-Berglund I, et al. Cancer risk in users of antimuscarinic drugs for overactive bladder: a cohort study in the Swedish National Registers (poster presentation). Abstract #919 in Abstracts of the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, The Convention Centre Dublin, Dublin, Ireland, August 25–28, 2016. Pharmacoepidemiol Drug Saf 2016;25:3–679.

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.