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Incidence of Common Cancers in Users of Antimuscarinic Medications for Overactive Bladder: A Danish Nationwide Cohort Study

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Abstract: The purpose of this study was to estimate the incidence rate (IR) of 10 common cancers in new users of antimuscarinic overactive bladder (OAB) medications. We conducted a cohort study using data recorded in Danish registers for patients newly exposed to the OAB drugs, darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium in years 2004–2012, aged ≥18 years and without cancer before treatment initiation. We estimated IRs for each study cancer (bladder, breast, colorectal, lung, melanoma, non-Hodgkin lymphoma, pancreas, prostate, renal and uterine), standardised by age and sex and explored IR trends over time since treatment initiation. For all cancer analyses, only the first incident targeted cancer was considered. Of 72,917 patients (60% women; mean age at treatment start: 66 years), 3475 developed a study cancer during 259,072 person-years of follow-up. The most common study cancers were prostate (48.1% of study cancers in men), breast (40.0% of study cancers in women) and lung (15.4% of all study cancers). The overall standardised study cancer IR was 5.4 per 1000 person-years (95% confidence interval, 5.3–5.6); IRs were similar across individual OAB drugs. The standardised IRs for bladder and prostate cancers, which have symptoms in common with OAB, were highest in the first 6 months of treatment initiation and lower thereafter. In contrast, IRs for other study cancers were nearly constant during follow-up. Cancer IRs did not vary substantially by individual OAB drug. Protopathic bias is a plausible explanation for the higher rates of bladder and prostate cancers observed soon after starting OAB drug treatment.

Overactive bladder syndrome (OAB) is defined as urgency with or without urge incontinence, usually experienced with frequent voiding and nocturia [1]. In Denmark, it has been reported that 7% of women aged 40–60 years had urge incontinence at least weekly and 30% had lower urinary tract symptoms [2]. The prevalence of the two conditions increased with age, most markedly for urge incontinence. Another study in Denmark reported a prevalence of urge incontinence occurring more than once per month of 19% among women with median age 75 years also increasing with age; the prevalence of urinary incontinence was 32% [3]. A systematic review found prevalences of urgency urinary incontinence between 2% and 31% in Europe, 2% and 36% in the United States, and 2% and 15% in Asia, based on surveys with slightly different wording, administered to populations with different age and sex distributions [4]. A survey in adults aged 18 years or older in Canada, Germany, Italy, Sweden, and the United Kingdom reported a prevalence of OAB of 12% [5].

Several antimuscarinic drugs to treat OAB have been available for many years and are widely used in Denmark [6]; yet, it is not known whether their risks for cancer differ. Therefore, in this study, we sought to estimate the incidence rates of commonly occurring cancers in patients treated for OAB with antimuscarinic drugs, using Danish nationwide registers. Additional analyses assessing cancer risk over time since start of treatment were also conducted to investigate the possibility of protopathic bias.

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Materials and Methods

Study design. We conducted a retrospective cohort study of adults newly exposed to antimuscarinic drugs used to treat OAB, using information collected in the Danish nationwide health registers. The study drugs were darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium. The study period was January 2004 through December 2012.

Data sources. We used routine healthcare information collected from Danish residents in five national registers linked using the Danish Person Registry number. Data were anonymised.

Dates of birth, death and migration were obtained from the Danish Person Registry [7]. Prescription data were obtained from the Danish National Prescription Registry, which contains data on all prescription drugs dispensed to Danish residents, whether prescribed by general practitioners or specialists and regardless of reimbursement status [8]. Data fields include substance name, quantity and date of dispensing. The Danish Cancer Registry provided records of all new cancer cases in the Danish population. Mandated reporting in this registry began in 1987 [9]. The Danish National Registry of Patients was accessed for data on medical care, including secondary care; data in this registry have been collected by public health authorities since 1977 [10]. Since 1995, outpatient diagnoses from hospitals have been systematically

included. Discharge diagnoses are coded according to the *International Classification of Diseases* (ICD-10 since 1994). The Cause of Death Registry provides information on the underlying and contributing causes of death of all residents of Denmark since 1875 [11].

Study population and follow-up. The study population included patients with at least 12 months of residence in Denmark, followed by an index prescription for a study drug, provided that the same drug was not prescribed during the previous 12 months and the patient was at least 18 years old at the dispensing date of the index prescription (i.e. the date of cohort entry). Patients with a cancer diagnosis other than non-melanoma skin cancer any time before the index prescription were excluded. Follow-up started on the date of the index prescription and finished at the earliest of the end of the study period, death, emigration or diagnosis of cancer other than non-melanoma skin cancer.

Study variables.

Exposure. This study examined exposure to the antimuscarinic OAB drugs, darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium, from dispensed prescriptions recorded in the Danish National Prescription Registry [8]. These drugs were available only by prescription during the study period.

Based on what is known about carcinogens, the effect of antimuscarinic OAB medications on the incidence of cancer, if any, was assumed to continue long after exposure. Therefore, after a dispensing for a study drug, person-time of ever exposure to that drug continued until the end of follow-up; person-time could be counted as exposed to more than one drug (groups are not mutually exclusive). Cumulative dose was categorised based on the number of dispensed defined daily doses (DDDs) [12] (0–199, 200–499, 500–999 and 1000 or more DDDs). As a sensitivity analysis, patients were considered exposed to a single OAB medication if they entered the cohort exposed to one

Table 1.
Patient characteristics at cohort entry by antimuscarinic OAB drug received at cohort entry, Denmark, 2004–2012.

Patient characteristics	Darifenacin 2698 n (%)	Fesoterodine 5749 n (%)	Oxybutynin 740 n (%)	Solifenacin 30,792 n (%)	Tolterodine 23,776 n (%)	Trospium 9105 n (%)	Multiple drugs 57 n (%)
Year of cohort entry							
2004	0 (0.0%)	0 (0.0%)	0 (0.0%)	310 (1.0%)	3679 (15.5%)	1129 (12.4%)	[1]
2005	3 (0.1%)	0 (0.0%)	62 (8.4%)	2067 (6.7%)	2933 (12.3%)	686 (7.5%)	[1]
2006	425 (15.8%)	0 (0.0%)	141 (19.1%)	1983 (6.4%)	2535 (10.7%)	680 (7.5%)	[1]
2007	710 (26.3%)	0 (0.0%)	199 (26.9%)	4140 (13.4%)	4004 (16.8%)	911 (10.0%)	5 (8.8%)
2008	557 (20.6%)	390 (6.8%)	92 (12.4%)	4226 (13.7%)	3043 (12.8%)	701 (7.7%)	9 (15.8%)
2009	380 (14.1%)	1292 (22.5%)	81 (10.9%)	4462 (14.5%)	2463 (10.4%)	889 (9.8%)	8 (14.0%)
2010	267 (9.9%)	1291 (22.5%)	64 (8.6%)	4343 (14.1%)	2058 (8.7%)	1567 (17.2%)	6 (10.5%)
2011	199 (7.4%)	1454 (25.3%)	62 (8.4%)	4580 (14.9%)	1662 (7.0%)	1422 (15.6%)	12 (21.1%)
2012	157 (5.8%)	1322 (23.0%)	39 (5.3%)	4681 (15.2%)	1399 (5.9%)	1120 (12.3%)	7 (12.3%)
Age at cohort entry (years)							
Median (interquartile range)	69 (59–78)	67 (56–76)	66 (55–76)	68 (57–77)	69 (58–78)	68 (56–77)	60 (41–71)
18-54	504 (18.7%)	1339 (23.3%)	175 (23.6%)	6415 (20.8%)	4498 (18.9%)	2066 (22.7%)	25 (43.9%)
55-64	523 (19.4%)	1155 (20.1%)	158 (21.4%)	6200 (20.1%)	4719 (19.8%)	1786 (19.6%)	10 (17.5%)
65-74	712 (26.4%)	1660 (28.9%)	201 (27.2%)	8304 (27.0%)	6194 (26.1%)	2386 (26.2%)	11 (19.3%)
75-84	671 (24.9%)	1143 (19.9%)	147 (19.9%)	6984 (22.7%)	5903 (24.8%)	2047 (22.5%)	10 (17.5%)
85+	288 (10.7%)	452 (7.9%)	59 (8.0%)	2889 (9.4%)	2462 (10.4%)	820 (9.0%)	[1]
Women	1768 (65.5%)	3407 (59.3%)	597 (80.7%)	18,353 (59.6%)	13,812 (58.1%)	5466 (60.0%)	31 (54.4%)
Diagnosis of obesity	176 (6.5%)	548 (9.5%)	64 (8.6%)	2215 (7.2%)	1327 (5.6%)	624 (6.9%)	[1]
Hypertension	561 (20.8%)	1416 (24.6%)	175 (23.6%)	6974 (22.6%)	5012 (21.1%)	1903 (20.9%)	10 (17.5%)
Alcohol abuse and alcohol-related conditions	137 (5.1%)	363 (6.3%)	38 (5.1%)	1822 (5.9%)	1407 (5.9%)	561 (6.2%)	[1]
Diabetes	207 (7.7%)	500 (8.7%)	55 (7.4%)	2413 (7.8%)	1881 (7.9%)	713 (7.8%)	[1]
Cardiovascular diseases[2]	608 (22.5%)	1323 (23.0%)	190 (25.7%)	7297 (23.7%)	6280 (26.4%)	2091 (23.0%)	16 (28.1%)
Dementia	61 (2.3%)	105 (1.8%)	25 (3.4%)	649 (2.1%)	613 (2.6%)	214 (2.4%)	[1]
Chronic pulmonary disease	268 (9.9%)	628 (10.9%)	89 (12.0%)	3274 (10.6%)	2364 (9.9%)	904 (9.9%)	7 (12.3%)
Connective tissue disease	147 (5.4%)	325 (5.7%)	38 (5.1%)	1557 (5.1%)	1096 (4.6%)	450 (4.9%)	5 (8.8%)
Organ transplantation	4 (0.1%)	23 (0.4%)	6 (0.8%)	119 (0.4%)	79 (0.3%)	27 (0.3%)	[1]
Hospitalisations before cohort entry (interquartile range)	14 (8–24)	18 (10–30)	19 (11–30)	16 (9–26)	14 (8–24)	15 (8–26)	30 (16–50)
Prescriptions before cohort entry							
Hormone replacement therapy	1237 (45.8%)	2286 (39.8%)	449 (60.7%)	11,931 (38.7%)	8370 (35.2%)	3522 (38.7%)	19 (33.3%)
Low-dose aspirin	994 (36.8%)	2053 (35.7%)	287 (38.8%)	11,280 (36.6%)	8829 (37.1%)	3209 (35.2%)	18 (31.6%)
Immunosuppressive agents	80 (3.0%)	196 (3.4%)	18 (2.4%)	871 (2.8%)	608 (2.6%)	243 (2.7%)	[1]

AMI, acute myocardial infarction; CV, cardiovascular; NSAIDs, non-steroidal anti-inflammatory drugs; OAB, overactive bladder.
[1]Fewer than five patients.
[2]AMI, stroke, transient ischaemic attack, coronary heart disease, heart failure or pulmonary artery disease.

Table 2.
Crude and standardised incidence rates of composite cancer end-point, by sex and OAB medication.

	Cancer cases	Individuals contributing person-time	Person-time (Years)	Crude incidence rate	95% CI	Standardised incidence rate	95% CI
Overall ever treated with							
Any OAB drug	3475	72,917	259,072	13.4	13.0–13.9	5.4	5.3–5.6
Darifenacin	236	4660	17,329	13.6	11.9–15.5	5.8	5.1–6.6
Fesoterodine	316	10,650	21,182	14.9	13.3–16.7	6.0	5.4–6.7
Oxybutynin	114	2614	10,201	11.2	9.2–13.4	6.0	5.0–7.2
Solifenacin	1680	38,754	122,765	13.7	13.0–14.4	5.6	5.4–5.9
Tolterodine	1552	27,609	119,418	13.0	12.4–13.7	5.2	5.0–5.5
Trospium	599	12,969	44,114	13.6	12.5–14.7	5.8	5.3–6.2
Women ever treated with							
Any OAB drug	1643	43,434	163,236	10.1	9.6–10.6	4.6	4.4–4.9
Darifenacin	141	3257	12,532	11.3	9.5–13.3	4.8	4.0–5.7
Fesoterodine	160	6631	13,686	11.7	9.9–13.6	5.3	4.5–6.2
Oxybutynin	77	2060	8195	9.4	7.4–11.7	4.8	3.8–6.0
Solifenacin	827	23,387	78,224	10.6	9.9–11.3	4.8	4.5–5.2
Tolterodine	730	16,173	74,612	9.8	9.1–10.5	4.6	4.3–4.9
Trospium	296	8092	28,573	10.4	9.2–11.6	4.8	4.3–5.4
Men ever treated with							
Any OAB drug	1832	29,483	95,835	19.1	18.3–20.0	6.2	6.0–6.5
Darifenacin	95	1403	4797	19.8	16.0–24.2	6.8	5.5–8.3
Fesoterodine	156	4019	7496	20.8	17.7–24.3	6.8	5.7–7.9
Oxybutynin	37	554	2006	18.4	13.0–25.4	7.2	5.1–10.0
Solifenacin	853	15,367	44,542	19.2	17.9–20.5	6.4	6.0–6.9
Tolterodine	822	11,436	44,806	18.3	17.1–19.6	5.9	5.5–6.3
Trospium	303	4877	15,541	19.5	17.4–21.8	6.7	6.0–7.5

CI, confidence interval; OAB, overactive bladder.
Incidence rates are per 1000 person-years. Table for ever exposure to OAB antimuscarinic drugs: person-time of ever exposure to each drug started with the beginning of exposure to each drug and continued until the end of follow-up; person-time could be counted as exposed to more than one drug (groups are not mutually exclusive). The reference for standardisation was the age and sex of the Danish population on 1 January 2008.

individual study medication and had no records for another study medication from the start of the prescription registry (1995) until the end of follow-up (groups are mutually exclusive).

End points. The cancer end points were 10 commonly occurring malignancies as individual end points and three composite cancer end-points, one combining women and men, one for women only and one for men only. Among women, the cancer end points were breast, lung and bronchus, colon and rectum, skin melanoma, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, corpus uteri and pancreas. Among men, study cancers were prostate, lung and bronchus, colon and rectum, skin melanoma, urinary bladder, non-Hodgkin lymphoma, kidney and renal pelvis, and pancreatic cancer. Cancer cases were ascertained from the Danish Cancer Registry [9]. For the majority of cancer diagnoses, including breast cancer, lung cancer, melanoma and colon cancer, more than 90% of tumours in the registry are histologically verified. For all cancer analyses, only the first incident targeted cancer was considered; subsequent or sequential targeted cancer events occurring in the same individual were ignored, and follow-up stopped at the occurrence of the first targeted cancer event.

Covariates. Patient characteristics, including demographics, lifestyle factors, prescription drug use and diagnoses, were ascertained using all data available before cohort entry from one or more of the five registers.

Statistical analyses. We estimated crude and age- and sex-standardised incidence rates (IRs) per 1000 person-years with 95% confidence intervals (CIs) for the composite cancer end points and for combined and individual OAB drugs in ever exposure and single exposure. The reference for standardisation was the age and sex composition of the Danish population as of 1 January 2008, from Statistics Denmark [13]. Results for individual cancer end points were also estimated as standardised IRs. Trends of cancer IRs related to time since cohort entry were assessed graphically by examining standardised IRs by 6-month intervals since cohort entry. This was of interest because symptoms reported by patients with undiagnosed genitourinary cancers, including prostate cancer and bladder cancer, may be confused with symptoms of OAB, and the pattern of time since start of OAB treatment until cancer diagnosis may be useful to differentiate between causality and other forms of association [14–17]. Trends for dose were assessed by examining standardised IRs in strata of cumulative dose; CIs were based on exact methods for Poisson distributions.

To eliminate a possible protopathic bias, we calculated standardised IRs with and without a 1-year lag time; that is, we disregarded the first year of follow-up after cohort entry. Then, to describe the relative incidence of cancer outcome, we calculated the standardised IR ratio (IRR), using tolterodine as a mutual reference for the other five OAB antimuscarinic drugs. These calculations were performed both with and without a 1-year lag time. The CIs for standardised IRRs were calculated by use of a two-sample Wald test.

This study did not require ethics committee review or notification, as retrospective register studies do not fall under the Danish definition of health science research. The study protocol was registered in the EU PAS Register before the start of data collection (EU PAS

Table 3.
Standardised incidence rates (95% confidence interval) for individual cancer types, by sex and OAB medication.

Cancer type	Any OAB drug	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium
Any study cancer							
Women	4.6 (4.4–4.9)	4.8 (4.0–5.7)	5.3 (4.5–6.2)	4.8 (3.8–6.0)	4.8 (4.5–5.2)	4.6 (4.3–4.9)	4.8 (4.3–5.4)
Men	6.2 (6.0–6.5)	6.8 (5.5–8.3)	6.8 (5.7–7.9)	7.2 (5.1–10.0)	6.4 (6.0–6.9)	5.9 (5.5–6.3)	6.7 (6.0–7.5)
Bladder							
Women	0.3 (0.2–0.3)	0.5 (0.3–0.9)	0.5 (0.3–0.8)	0.3 (0.1–0.6)	0.3 (0.2–0.4)	0.3 (0.2–0.3)	0.3 (0.2–0.5)
Men	1.0 (0.9–1.1)	1.0 (0.6–1.7)	1.3 (0.9–1.9)	2.6 (1.2–4.7)	1.4 (1.2–1.6)	0.9 (0.7–1.1)	0.8 (0.6–1.1)
Breast							
Women	2.1 (1.9–2.2)	2.3 (1.8–3.0)	3.2 (2.6–3.9)	2.8 (2.0–3.8)	2.3 (2.1–2.6)	2.2 (1.9–2.4)	2.5 (2.1–2.9)
Colorectal							
Women	0.6 (0.5–0.6)	0.7 (0.4–1.0)	1.0 (0.7–1.4)	0.6 (0.3–1.1)	0.6 (0.5–0.8)	0.6 (0.5–0.7)	0.7 (0.5–0.9)
Men	0.7 (0.6–0.8)	0.5 (0.3–1.0)	1.4 (0.9–2.0)	0.8 (0.3–1.7)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.8 (0.6–1.2)
Kidney/renal pelvis							
Women	0.1 (0.1–0.2)	0.2 (0.1–0.5)	0.2 (0.1–0.5)	0.1 (0.0–0.5)	0.2 (0.1–0.3)	0.1 (0.1–0.2)	0.1 (0.0–0.2)
Men	0.1 (0.1–0.2)	0.0 (0.0–0.2)	0.2 (0.1–0.4)	0.3 (0.0–1.1)	0.2 (0.1–0.3)	0.1 (0.1–0.2)	0.1 (0.1–0.3)
Lung/bronchus							
Women	0.7 (0.6–0.8)	0.6 (0.4–1.0)	1.1 (0.8–1.6)	1.1 (0.6–1.7)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.7 (0.5–1.0)
Men	0.9 (0.8–1.0)	1.5 (0.9–2.3)	1.3 (0.9–1.8)	1.0 (0.5–2.1)	0.9 (0.8–1.1)	0.7 (0.6–0.9)	0.8 (0.6–1.0)
Melanoma							
Women	0.3 (0.2–0.4)	0.4 (0.2–0.8)	0.5 (0.3–0.9)	0.3 (0.1–0.7)	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.4 (0.2–0.6)
Men	0.3 (0.2–0.4)	0.1 (0.0–0.4)	0.4 (0.2–0.7)	0.7 (0.1–2.5)	0.3 (0.2–0.4)	0.4 (0.3–0.5)	0.5 (0.3–0.8)
Non-Hodgkin lymphoma							
Women	0.1 (0.1–0.2)	0.1 (0.0–0.3)	0.2 (0.1–0.5)	0.1 (0.0–0.4)	0.2 (0.1–0.2)	0.1 (0.0–0.1)	0.1 (0.1–0.3)
Men	0.1 (0.1–0.2)	0.1 (0.0–0.4)	0.2 (0.1–0.5)	1.1 (0.0–6.0)	0.2 (0.1–0.3)	0.2 (0.1–0.2)	0.3 (0.1–0.5)
Pancreas							
Women	0.2 (0.1–0.2)	0.1 (0.0–0.2)	0.1 (0.0–0.3)	0.3 (0.1–0.6)	0.2 (0.2–0.3)	0.2 (0.1–0.2)	0.3 (0.1–0.4)
Men	0.2 (0.2–0.3)	0.1 (0.0–0.4)	0.3 (0.1–0.6)	0 (0.0–1.8)	0.2 (0.2–0.3)	0.2 (0.1–0.2)	0.4 (0.2–0.7)
Prostate							
Men	2.9 (2.7–3.1)	4.4 (3.3–5.7)	6.3 (5.2–7.4)	3.4 (2.1–5.1)	3.4 (3.1–3.7)	3.1 (2.8–3.4)	3.9 (3.3–4.5)
Uterus							
Women	0.3 (0.2–0.4)	0.3 (0.1–0.6)	0.3 (0.1–0.5)	0.4 (0.1–0.7)	0.4 (0.3–0.5)	0.3 (0.2–0.4)	0.2 (0.1–0.3)

OAB, overactive bladder.
Incidence rates are per 1000 person-years. Table for ever exposure to OAB antimuscarinic drugs: person-time of ever exposure to each drug started with the beginning of exposure to each drug and continued until the end of follow-up; person-time could be counted as exposed to more than one drug (groups are not mutually exclusive). The reference for standardisation was the age and sex of the Danish population on 1 January 2008.

Register No: EUPAS8441) [18]. Analyses were performed with Stata for Windows, version 13 (StataCorp LLC, College Station, TX, USA).

Results

The study population comprised 72,917 patients followed from January 2004 through December 2012 (table 1). The mean age at cohort entry was 66 years, and 59% of patients were aged 65 years or older; 60% were women. The most commonly prescribed study drugs at cohort entry were solifenacin, tolterodine and trospium. Around 1% entered the cohort on oxybutynin, and <1% entered the cohort on multiple OAB medications. Patients who entered the cohort on oxybutynin had a higher proportion of women than patients on other treatments.

Overall, 3475 patients (4.8%) developed study cancers during 259,072 person-years of follow-up (table 2); 52.7% of study cancers occurred in men. The most commonly occurring study cancers were prostate (881 cancer cases; 48.1% of study cancers in men), breast (658 cases; 40.0% of study cancers in women), lung (534 cases; 15.4% of all study cancers), colorectal (434 cases; 12.5% of all study cancers) and bladder (369 cases; 10.6% of all study cancers).

Standardised incidence rates for ever exposure to study OAB medications.

In women, the standardised IR per 1000 person-years (95% CI) for the sex-specific composite cancer end-point ranged from 4.6 (4.3–4.9) for tolterodine to 5.3 (4.5–6.2) for fesoterodine (table 2). In men, it ranged from 5.9 (5.5–6.3) for tolterodine to 6.8 for darifenacin (5.5–8.3) and fesoterodine (5.7–7.9).

Within individual cancer types, standardised IRs were generally similar among patients ever exposed to various study drugs, with a few exceptions (table 3). The standardised IR for prostate cancer in men ever exposed to fesoterodine was higher than for those ever exposed to solifenacin, tolterodine or trospium; darifenacin had an intermediate rate. The standardised IR for breast cancer in women ever exposed to fesoterodine was higher than that for other drugs. The standardised IR for colorectal cancer was higher in women and men ever exposed to fesoterodine than for other drugs. For the less common cancer types, confidence intervals for estimates for individual drugs were wide, which was also true for most analyses on oxybutynin (used by 1% of patients).

Table 4.
Crude and standardised incidence rates of composite cancer end-point in patients exposed to a single drug, by sex and OAB medication.

	Cancer cases	Individuals contributing person-time	Person-time (Years)	Crude incidence rate	95% CI	Standardised incidence rate	95% CI
Overall ever treated with							
Any OAB drug	2483	51,956	158,716	15.6	15.0–16.3	6.2	6.0–6.4
Darifenacin	96	1753	6033	15.9	12.9–19.4	6.7	5.4–8.1
Fesoterodine	137	4476	8414	16.3	13.7–19.2	6.6	5.6–7.9
Oxybutynin	12	317	1081	11.1	5.7–19.4	4.8	2.5–8.5
Solifenacin	989	23,368	64,650	15.3	14.4–16.3	6.2	5.8–6.6
Tolterodine	982	16,349	62,827	15.6	14.7–16.6	6.0	5.6–6.4
Trospium	267	5693	15,711	17.0	15.0–19.2	7.0	6.2–7.9
Women ever treated with							
Any OAB drug	1073	29,589	94,935	11.3	10.6–12.0	5.3	4.9–5.6
Darifenacin	46	1078	3861	11.9	8.7–15.9	5.1	3.7–6.8
Fesoterodine	56	2555	5030	11.1	8.4–14.5	5.2	4.0–6.8
Oxybutynin	6	245	846	7.1	2.6–15.4	2.7	1.0–6.0
Solifenacin	436	13,346	38,583	11.3	10.3–12.4	5.3	4.8–5.8
Tolterodine	414	9103	37,328	11.1	10.0–12.2	5.2	4.7–5.7
Trospium	115	3262	9288	12.4	10.2–14.9	6.0	4.9–7.2
Men ever treated with							
Any OAB drug	1410	22,367	63,781	22.1	21.0–23.3	7.2	6.8–7.5
Darifenacin	50	675	2173	23.0	17.1–30.3	8.3	6.1–10.9
Fesoterodine	81	1921	3384	23.9	19.0–29.8	8.1	6.4–10.0
Oxybutynin	6	72	235	25.5	9.4–55.6	7.0	2.6–15.2
Solifenacin	553	10,022	26,067	21.2	19.5–23.1	7.1	6.5–7.7
Tolterodine	568	7246	25,498	22.3	20.5–24.2	6.8	6.3–7.4
Trospium	152	2431	6423	23.7	20.1–27.7	8.1	6.8–9.5

CI, confidence interval; OAB, overactive bladder.
Incidence rates are per 1000 person-years. Table for ever exposure to a single OAB antimuscarinic drug. Single drug exposure was defined by having no recorded prescriptions for other OAB drugs from 1995 until the end of follow-up or occurrence of the first cancer end-point, whichever came first (groups are mutually exclusive). The reference for standardisation was the age and sex of the Danish population on 1 January 2008.

Standardised incidence rates by single exposure to study OAB medications.

Among the 51,956 patients (71%) with ever exposure to a single study medication, 2483 study cancers occurred during 158,716 person-years of follow-up (crude IR, 15.6 per 1000 person-years; 95% CI, 15.0–16.3) (table 4). Except for oxybutynin (with only six exposed cancer cases in women and six in men), standardised IRs for the composite cancer end-point, overall and by sex, were similar across drugs. For individual cancer types, standardised IRs did not show consistent trends of increased risk for any study drug (table S1).

Analyses by time since cohort entry and cumulative dose.

Standardised IRs for all cancers combined and for bladder and prostate cancers individually tended to decrease over time since cohort entry (figs. 1 and S1). The standardised IR for men and women combined for bladder cancer was highest <6 months after cohort entry, lower 6–11 months after cohort entry and decreased thereafter. The standardised IR for prostate cancer was also highest <6 months after cohort entry, lower 6–11 months after cohort entry and lower thereafter. In contrast, standardised IRs of other cancers did not show this effect of time since cohort entry. We observed a decreasing cancer risk with increasing cumulative dose for all study drugs except darifenacin (table S2).

As expected, the standardised IRs were all lower with the application of a 1-year lag time than without (table 5). The standardised IRRs were all close to the unity with nearly all CIs including the null estimate. The only exception was fesoterodine, which showed a marginally higher cancer IR than tolterodine in the analysis without lag time (standardised IRR, 1.2; 95% CI, 1.0–1.3). This estimate came closer to the null with the introduction of a lag time (1.1 [0.9–1.3]).

Discussion

In this cohort of patients treated with antimuscarinic OAB medications, a majority of patients were women and used only one drug during follow-up. Although some of the analyses suggested a higher risk of individual cancer end points among patients exposed to fesoterodine, results from single-exposure analyses did not confirm this finding. For bladder and prostate cancers, an increased risk was found during the early months after treatment initiation. We did not observe increasing trends in cancer risks over time, and we observed generally decreasing trends with increasing cumulative dose, which argues strongly against a cancer-causing or cancer-promoting effect. Furthermore, the trend of decreasing IRs for bladder and prostate cancer over time since first exposure suggests protopathic bias; that is, the OAB medication was used to treat symptoms that were actually early

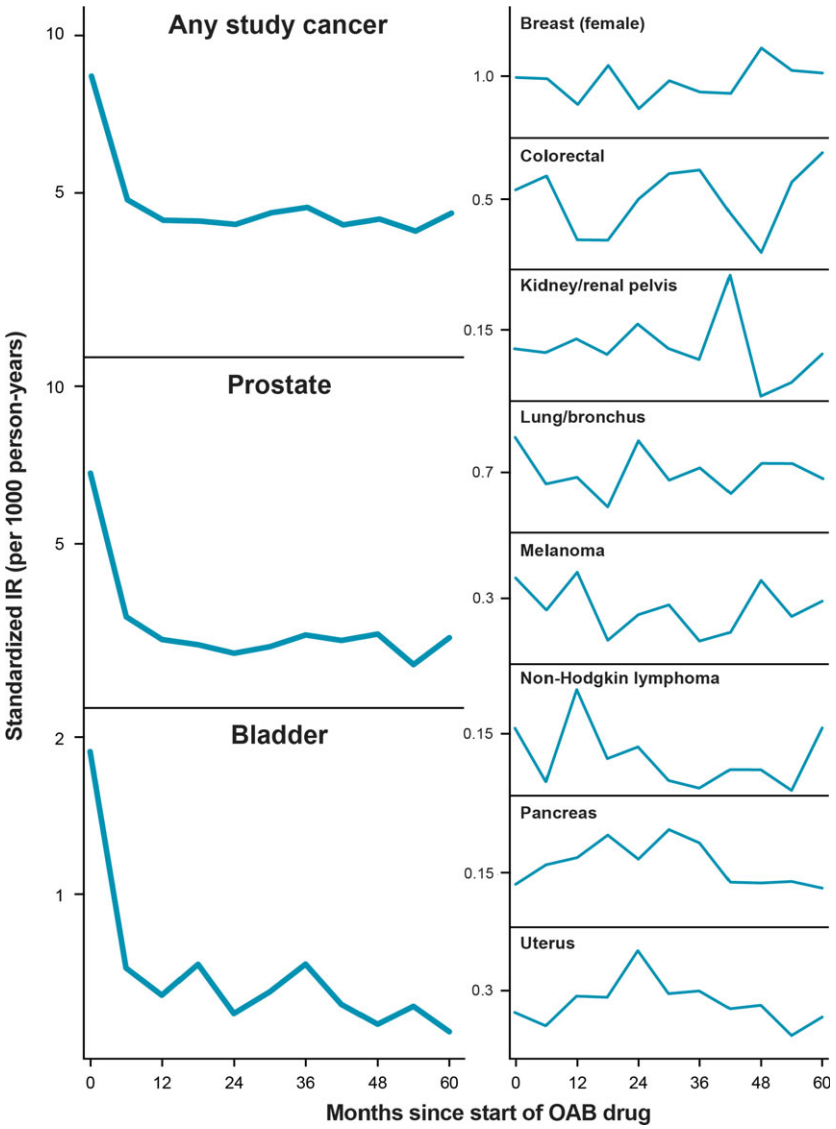

Fig. 1. Standardised cancer incidence rates by time since cohort entry. More detailed figures showing these standardised incidence rates with confidence intervals are presented in the Supporting Information. IR, incidence rate; OAB, overactive bladder.

Table 5.

Standardised incidence rates and ratios for the composite cancer outcome.

	All follow-up included		1-year lag time applied	
Antimuscarinic OAB drug	Standardised IR (95% CI)	Standardised IRR (95% CI)	Standardised IR (95% CI)	Standardised IRR (95% CI)
Tolterodine	5.2 (5.0–5.5)	1.0 (reference)	4.9 (4.6–5.2)	1.0 (reference)
Darifenacin	5.8 (5.1–6.6)	1.1 (1.0–1.3)	4.9 (4.2–5.7)	1.0 (0.9–1.2)
Fesoterodine	6.0 (5.4–6.7)	1.2 (1.0–1.3)	5.3 (4.6–6.1)	1.1 (0.9–1.3)
Oxybutynin	6.0 (5.0–7.2)	1.2 (1.0–1.4)	5.0 (4.0–6.1)	1.0 (0.8–1.3)
Solifenacin	5.6 (5.4–5.9)	1.1 (1.0–1.2)	5.0 (4.7–5.3)	1.0 (0.9–1.1)
Trospium	5.8 (5.3–6.2)	1.1 (1.0–1.2)	5.3 (4.8–5.8)	1.1 (1.0–1.2)

CI, confidence interval; IR, incidence ratio; IRR, incidence rate ratio.

Incidence rates are per 1000 person-years. Table for ever exposure to overactive bladder antimuscarinic drugs: person-time of ever exposure to each drug started with the beginning of exposure to each drug and continued until the end of follow-up; person-time could be counted as exposed to more than one drug (groups are not mutually exclusive). The reference for standardisation was the age and sex of the Danish population on 1 January 2008. For the standardised incidence rate ratios, tolterodine was used as a mutual reference. The analysis was conducted with and without a 1-year lag time applied.

symptoms of cancer, leading to detection shortly after treatment initiation. Bias due to heightened attention to urinary tract symptoms shortly after starting OAB therapy is a less likely explanation for the early peak in bladder and prostate cancer: the duration of elevated rates of these cancers (about a year) is not long enough for a new cancer to develop and be detected through surveillance that is unrelated to workup of the symptoms the patient had at the time of treatment initiation. Cancers likely to be found coincidentally due to routine surveillance are breast, colon and prostate cancer; there was no indication of increased rates of breast or colon cancer diagnoses during the first months of treatment.

One of the most striking results of our analysis is the profound temporal dependency of the IR of prostate and bladder cancer, while no such temporality exists for the other cancer sites. The period of elevated cancer incidence appears to be approximately 6 months. This pattern is highly suggestive of protopathic bias; the early symptoms of bladder or prostate cancer are misinterpreted as overactive bladder and treated accordingly. With some delay, the cancer diagnosis is eventually established, but as the symptomatic drug use preceded the diagnosis, it may be erroneously perceived as a potential cause. Indeed, it has been shown that such protopathic bias has a typical time horizon of 6 months [16].

We are not aware of biological considerations that might explain why users of any one drug in the class would experience an increased cancer risk. Fesoterodine was introduced to the Danish market in 2008, later than the other medications. The observed tendency for some cancer IRs to decrease with increasing time as first exposure to OAB medications might explain the higher rates observed for fesoterodine. Due to its relatively shorter presence in the market, we are observing the early increased IRs with fesoterodine (as with the older drugs) but a relatively short period of low IRs (which is longer for the older drugs). This explanation is supported by the observation that IRs in strata of cumulative dose for fesoterodine do not seem to be higher than for other drugs (table S2). In the comparative analysis, with results around the unity, we used age- and sex-standardised IRs, thereby removing confounding by age and sex. Other covariates are well balanced and unlikely to confound our relative comparison.

Registry procedures and findings around validity and completeness of cancer registration have been documented [19]. Since 2004, all cancers in the Danish National Registry of Patients are routinely reported to the Danish Cancer Registry. For the cancer types included in this study, more than 90% are histologically verified [19].

Limitations of this study include the possibility that dispensed medication is not used. Given the patient copayment, this is unlikely to be extensive, and there is no reason why non-use would affect one study drug more than others. For our analyses on single drug use, we excluded patients who started on one drug and then changed to another. This would raise concerns whether patients changed to a second OAB drug differentially across study drugs in relation to either high or low cancer risk. Based on current knowledge, this seems unlikely. Adjustment for potential confounders is limited in the estimates we present (age and sex only). Although we did not see important differences across users of the study medications, more complete adjustment is planned for the next phase of this study. The interpretation of our findings on oxybutynin is limited by the low prevalence of use of the drug. Results on the composite cancer end points are driven by results from the most frequent cancer sites.

Use of the Danish registers is a strength of this study because these data sources cover the entire Danish population, which is critical for obtaining valid incidence rates. The use of census data enabled tracking of all patients and accounted for migration into or out of the population [7]. Another strength of this study is that we compared users of different OAB medications rather than users and non-users, thus reducing confounding at the design stage.

In conclusion, these results suggest that the levels of cancer risk associated with the antimuscarinic OAB medications evaluated in this study are similar to one another. Decreasing prostate and bladder cancer IRs over time since first use suggests protopathic bias.

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Conflict of Interest

This study is a post-marketing regulatory requirement from the United States Food and Drug Administration and was funded by Astellas Pharma Global Development, Inc. The contract provides the research team independent publication rights, in accordance with the European Medicines Agency's *Guideline on Good Pharmacovigilance Practices (GVP)*, Module VIII, Section VIII.B.5. Andrea Margulis, James Kaye, Susana Perez-Gutthann, and Alejandro Arana are employees of RTI International, an independent non-profit research organisation that does work for government agencies and pharmaceutical companies. Jesper Hallas, Nina Sahlertz Kristiansen and Anton Pottegård have worked on a project commissioned by Astellas, with funding paid to their employer. Willem Jan Atsma, Kwame Appenteng and Stefan de Vogel are employees of Astellas Pharma Global Development, the sponsor of this study.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Standardised cancer incidence rates by time since cohort entry.

Table S1. Standardised incidence rates (95% confidence interval) for individual cancer types, by sex and OAB medication (single drug exposure).

Table S2. Crude and standardised incidence rates of composite cancer endpoint, by OAB medication and cumulative dose.