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ORIGINAL RESEARCH

Exposure to antimuscarinic medications for treatment of overactive bladder and risk of lung cancer and colon cancer

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Introduction: One out of six adults has symptoms of overactive bladder (OAB). Antimuscarinic medication is the main pharmacological group used in the treatment of OAB. In preclinical studies, antimuscarinic compounds have been found to inhibit cell proliferation in lung cancer and colon cancer.

Objective: The aim of this study was to investigate the association between exposure to antimuscarinic medication and the risk of lung cancer and colon cancer.

Methods: Individuals in Sweden who first filled a prescription for an antimuscarinic medication used to treat OAB (ie, oxybutynin, solifenacin, darifenacin, fesoterodine, or tolterodine) between July 1, 2006, and December 31, 2012, were identified and classified as exposed. Each exposed individual was individually matched with up to ten unexposed individuals from the Swedish general population, based on year of birth, sex, and county of residence. Cox proportional hazard models with follow-up time as the underlying time scale were used to estimate HRs with 95% CIs.

Results: In total, 164,000 exposed and 1,446,472 unexposed individuals were included in this study. The estimated HRs for lung cancer, in follow-up time intervals of <1 year, 1–4 years, and ≥4 years, were as follows: 0.86 (95% CI: 0.75–0.98), 0.63 (95% CI: 0.56–0.70), and 0.43 (0.34–0.55), respectively. The corresponding estimates for colon cancer were as follows: 0.91 (95% CI: 0.80–1.03), 0.81 (95% CI: 0.74–0.88), and 0.61 (95% CI: 0.51–0.73), respectively.

Conclusion: There was an inverse association between exposure to antimuscarinic medications, used in the treatment of OAB, and a diagnosis of colon cancer or lung cancer, which is in line with the findings in preclinical studies.

Keywords: overactive bladder, antimuscarinic medications, lung cancer, colon cancer

Introduction

Overactive bladder (OAB) is defined as urgency with or without incontinence, usually with frequency and nocturia.[1] One out of six adults has symptoms of OAB, and the prevalence increases with age and is more common among women than among men.[2,3] Alzheimer's disease, previous stroke, overweight, and obesity are important risk factors for OAB.[4,5]

Antimuscarinic medication is the main pharmacological group used in the treatment of OAB, and the selected study medications are solely approved for OAB in Sweden.[6] Antimuscarinic medications can also be used in other conditions, eg, asthma. They act by blocking acetylcholine from binding to the muscarinic receptors present on the detrusor muscle, resulting in a decreased contraction of the bladder.[6,7] In preclinical

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studies, activation of the muscarinic receptor subtype 3 (M3) by acetylcholine, or other M3-receptor agonists, has been shown to affect cell proliferation and cancer cell growth in prostate, colon, pancreatic, lung, brain, breast, ovarian, skin (melanocytes), stomach, bone, and blood (lymphoma and leukemia).[8–21] Preclinical studies have also shown that inhibition of the M3-receptor by antagonists inhibits cell proliferation in lung cancer (both small-cell lung cancer and non-small-cell lung cancer) and colon cancer.[22–26] These findings suggest that muscarinic antagonists may have an inhibitory effect on cell proliferation and cancer cell growth in the lung and colon in humans.

Smoking, exposure to radon and asbestos, and genetic factors are well-established risk factors for lung cancer.[28] Inflammatory intestinal conditions, diet, a sedentary lifestyle, obesity smoking, and alcohol are risk factors for colon cancer.[29,30]

To the best of our knowledge, this is one of the first studies with data from population-based registers investigating the association between antimuscarinics for OAB and the risk of lung cancer and colon cancer.[27] A Danish study, including 72,917 patients, investigated the association between antimuscarinic medications for OAB and different cancers, including lung cancer and colon cancer, and estimated age- and sex-standardized incidence rates (SIRs) for the associations, and the findings indicated a protective effect.[27] However, as SIRs are less precise measures as compared to HRs, we will use HRs to assess associations between exposure to antimuscarinics and the risk of lung cancer and colon cancer.

The aim of the study was to investigate the association.

Patients and methods

Study population

The exposed individuals in the study population were patients in Sweden who first filled a prescription for an antimuscarinic medication used to treat OAB (ie, oxybutynin, solifenacin, darifenacin, fesoterodine, or tolterodine) between July 1, 2006, and December 31, 2012. A new user was defined as a patient who filled the first prescription for a study medication, without a filled prescription for a study medication during the previous 12 months. The first filled prescription had to be for a tablet formulation to enable calculation of accumulated use.

To ensure a homogeneous study population, only antimuscarinic medications solely approved for the treatment of OAB were included.

Each exposed eligible individual was individually matched with up to ten unexposed individuals with the same characteristics such as year of birth, sex, county of residence, and vital status.

Individuals, both exposed and unexposed, younger than 18 years at the time of the first filled prescription, with a history of lung cancer or colon cancer at any time before the first filled prescription, were excluded from the study cohort. A look back period of 5 years was used to identify comorbid conditions.

Data sources

All Swedish residents are assigned a unique personal identification number (PIN) at birth or upon immigration, which is kept unchanged throughout life.[31,32] The information from the different registers was linked using the PIN.

Data on filled prescriptions were obtained from the Swedish Prescribed Drug Register (PDR) with information available from July 2005, on filled prescriptions from community pharmacies. The PDR contains information on the substance name, product name, formulation, amount, date of prescribing and date of filling the prescription, and the prescriber's profession.[33] The PDR does not include data on over-the-counter medications or medications on requisition used in hospitals or nursing homes.

The Swedish Cancer Register (SCR) was used to identify individuals with a diagnosis of lung cancer or colon cancer, both for exclusion and to identify the end points. The SCR was established in 1958 and records individual data on all newly diagnosed malignant tumors in Sweden.[34] The register uses the ICD 7th revision (ICD-7). Since 2005, the site and histological type of the cases have been coded in ICD Oncology third edition (ICD-O-3) codes.[35]

The National Patient Register (NPR) and the PDR were used to obtain information on comorbid conditions (ie, cerebrovascular disease, COPD, diabetes mellitus [type 1 or 2], hypertension, inflammatory bowel disease, peptic ulcer disease, and obesity) for up to 5 years before the date of the first filled prescription. The data on filled prescriptions from the PDR were used as proxies for a diagnosis of hypertension, diabetes mellitus, or obesity. The specific medications used as proxies are listed in Table S1. The NPR started collecting data in 1964 and has national coverage regarding in-patient care since 1987.[36,37] Since 2001, information on outpatient visits is also recorded and the coverage increased over subsequent years. Primary care is not covered in the register. For each admission, the NPR records information on health care establishment, date, duration of care, and personal data (sex, age, PIN, and place of residence) and contains a main and up to 30 contributory diagnoses using

ICD codes. From 1997 the tenth revision of the ICD codes (ICD-10) is used in the NPR.

Information for censoring individuals who died was obtained from the Swedish Cause of Death Register (CDR). The CDR was established in 1961 and records causes of death of Swedish citizens independently of whether the death occurred in Sweden or abroad.[38] Data on income, education, and emigration were obtained from the population registers held by Statistics Sweden.[39,40]

End points and follow-up

Primarily, ICD-O-3 codes were used to identify the end points, and the ICD-7 codes were used in the case of missing ICD-O-3 codes. The two end points of interest were diagnoses of colon cancer (ICD-7 code 153 and ICD-O-3 code C18) and lung cancer (ICD-7 codes 162.1 and 163, and ICD-O-3 codes C34 and C39).

This was an intention-to-treat analysis and follow-up started at the date of the first filled prescription between July 1, 2006, and December 31, 2012 (index date). Follow-up ended on the date of one of the following events: a filled prescription for a non-tablet formulation of a study medication, death, a diagnosis of one of the cancer end points of interest, date of emigration, or on December 31, 2013, whichever occurred first. Follow-up of the unexposed individuals started on the same day as for the exposed individual they were matched to.

Statistical analysis

The standardized difference was calculated to quantify the difference in demographics and clinical characteristics between the compared groups, defined as the difference in the mean between the two groups divided by the SD.[41]

Continuous variables are presented with median and IQR or with mean and SD, whereas categorical variables are presented as numbers and proportions.

Differences in the incidence of the two cancers of interest between exposed and unexposed were compared by estimating incidence rate difference (IRD) and 95% CIs.

Cox proportional hazard models, with follow-up time as the underlying time scale, were used to estimate HRs with 95% CIs for the association between exposure and the cancer end points of interest. HRs were estimated using unadjusted, base, and fully adjusted models. The base model was adjusted for the matching variables by stratification. The full model was additionally adjusted for "a priori" selected variables, such as income, the level of attained education the year before the cohort inclusion date, and smoking status using a COPD diagnosis or a filled prescription for smoking cessation medication during up to 5 years prior to the index date as a proxy.[42] In addition, all the reported comorbidities, Charlson comorbidity index,[43] history of any cancer, and the number of observations in the NPR were evaluated for inclusion in the full model and only included in the model if they changed the point estimate by at least 10%.[44] Analyses were done overall, and stratum-specific by sex, follow-up time, and index year. In addition, overall analyses were performed using a 6-month lag time and a 12-month lag time. The proportional hazard assumption was tested for all analyses, and if violated, an interaction term between the exposure status and the follow-up time was included in the model.

A separate analysis that included only the exposed individuals was performed to compare individuals by cumulative defined daily dose (DDD) intervals (≤90, 91–182, 183–364, and ≥365). In this analysis, the person time contributed by each exposed individual was separated by subsequent and cumulative DDD intervals.

A sensitivity analysis was performed and included patients who started treatment with tolterodine, which is the most common antimuscarinic medication for the treatment of OAB in Sweden. Apart from the criteria for end of follow-up used in the main analysis, a filled prescription for a study medication other than tolterodine was added in the sensitivity analysis.

All data were analyzed with SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 14 (StataCorp LP, College Station, TX, USA).

Ethical approval

This study was approved by the regional ethical board in Stockholm, Sweden (record numbers 2014/1478-31 and 2015/1669-32).

Results

Descriptive data

Overall, 253,406 exposed individuals were identified in the PDR (Figure 1). Of those, 86,980 were considered to be prevalent users, 7 were excluded due to invalid data, 276 were younger than 18 years, and further 2,143 were excluded due to the diagnosis of lung cancer or colon cancer before the index date. In total, 164,000 exposed individuals were included. The exposed individuals were individually matched to a total of 1,491,548 unexposed individuals. There were 1,446,472 unexposed individuals included in the study after applying the exclusion criteria. On average, 8.8 unexposed individuals were matched to each exposed individual.

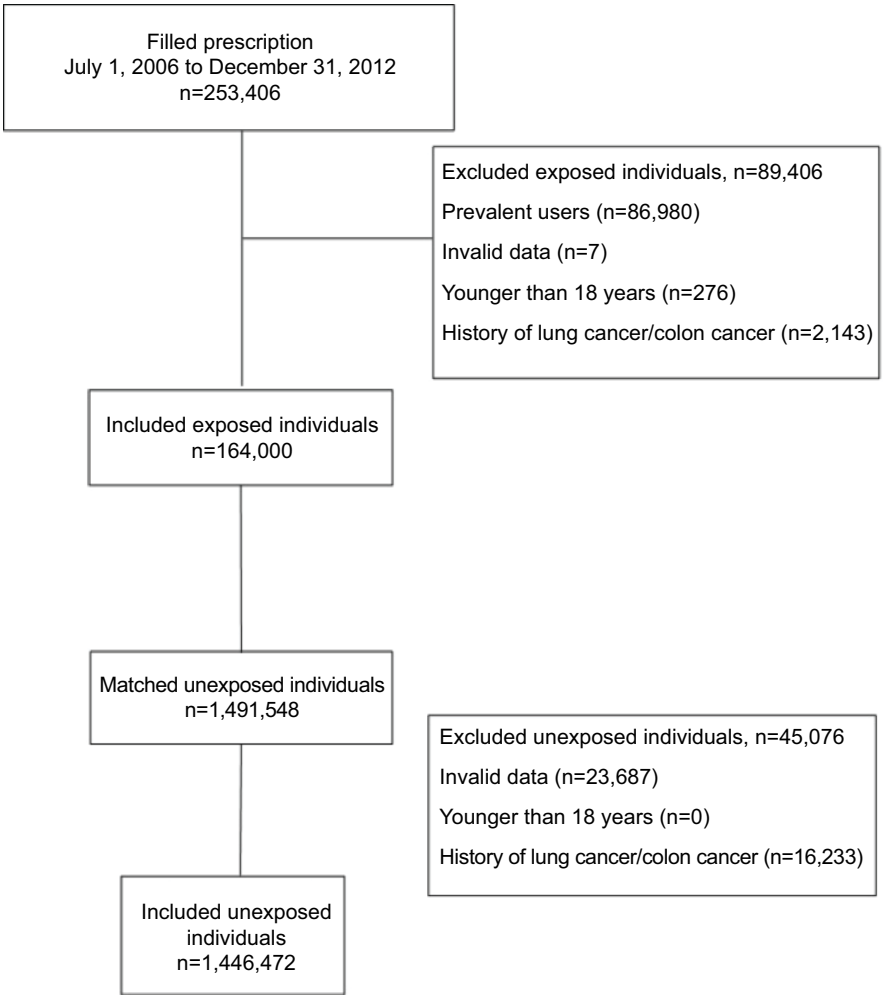

Figure 1 Inclusion of study population to the study cohort.

Among the exposed, 57.0% were women, with a corresponding proportion of 54.3% in the unexposed group (Table 1). The median age at index was 69 years in the exposed group and 68 years in the unexposed group. The median follow-up time, for both groups, was 47 months. A diagnosis of OAB was recorded in the NPR for 5.5% of the exposed individuals and for 1.2% of the unexposed individuals. The most common comorbid condition, in both groups, was hypertension, which was present in 45.6% of the exposed group and 39.0% in the unexposed group, with a standardized difference of 13%. All the investigated comorbid conditions were more common among the exposed individuals.

Outcomes

There were 659 (0.4%) and 911 (0.6%) exposed individuals who developed lung cancer and colon cancer, respectively (Table 2). The corresponding numbers in the unexposed group were 8,394 (0.6%) for lung cancer and 9,537 (0.7%) for colon cancer. The estimated IRD for lung cancer was –44.9 per 100,000 person-years (95% CI: −53.3, –36.5) and for colon cancer –26.1 per 100,000 person-years (95% CI: −35.8, –16.3) (Table 1).

Lung cancer

The point estimates and 95% CIs of the HRs for the overall analysis of lung cancer in the three different intervals with time since index date (<1 year, 1–4 years, and ≥4 years) were 0.86 (95% CI: 0.75–0.98), 0.63 (95% CI: 0.56–0.70), and 0.43 (0.34–0.55), respectively (Table 2). When applying lag times, a tendency of decreasing point estimates was observed compared to the overall HRs observed in the main analysis, for which no lag time was used (Table S2).

In the stratum-specific analysis by sex, the observed point estimates of the HRs for men were all <1 in the follow-up time intervals (<1 year, 1–4 years, and ≥4 years): 0.90 (95% CI: 0.75–1.08), 0.62 (95% CI: 0.53–0.72), and 0.51 (95%

Table 1 Demographics and clinical characteristics of study subjects, both exposed and unexposed individuals

Variables	Exposed	Unexposed	d[a]
Total number of individuals	164,000	1,446,472	
Age at index (years)			0.08
Mean (SD)	67 (15)	66 (15)	
Median (q1–q3)	69 (60–78)	68 (58–77)	
Follow-up time (months)			0.00
Mean (SD)	47 (24)	47 (24)	
Median (q1–q3)	47 (27–68)	47 (27–68)	
Sex, n (%)			
Women	93,440 (57.0)	785,928 (54.3)	0.05
Men	70,560 (43.0)	660,544 (45.7)	–0.05
Index year, n (%)			
2006–2008	71,057 (43.3)	625,357 (43.2)	0.00
2009–2010	48,060 (29.3)	421,824 (29.2)	0.00
2011–2012	44,883 (27.4)	399,291 (27.6)	0.00
Education (highest completed), n (%)			
Mandatory or less (≤9 years)	39,815 (24.2)	366,988 (25.4)	–0.03
Upper secondary (10–12 years)	55,416 (33.8)	494,258 (34.2)	–0.01
Higher education (>12 years)	35,168 (21.4)	319,865 (22.1)	–0.02
No educational data	33,601 (20.6)	265,361 (18.3)	0.06
Income (quartiles from overall population), n (%)			
q1	41,137 (25.1)	361,367 (25.0)	0.00
q2	44,442 (27.1)	358,064 (24.8)	0.05
q3	41,222 (25.2)	361,277 (25.0)	0.00
q4	36,918 (22.5)	365,587 (25.3)	–0.07
Diagnosis of overactive bladder, n (%)	9,093 (5.5)	16,882 (1.2)	0.24
Comorbid conditions, n (%)			
Cerebrovascular disease	12,538 (7.6)	82,593 (5.7)	0.08
COPD	4,657 (2.8)	33,544 (2.3)	0.03
Diabetes mellitus (type 1 or 2)	19,278 (11.8)	141,221 (9.8)	0.06
Hypertension	74,840 (45.6)	563,678 (39.0)	0.13
Inflammatory bowel disease	1,632 (1.0)	11,524 (0.8)	0.02
Peptic ulcer disease	2,716 (1.7)	16,776 (1.2)	0.04
Obesity	957 (0.6)	4,577 (0.3)	0.04
Incidence rate difference per 100,000 person-years			
Lung cancer	–44.9 (95% CI: –53.3, –36.5)		–
Colon cancer	–26.1 (95% CI: –35.8, –16.3)		–

Note: [a]Standardized difference.

CI: 0.37–0.70), respectively (Table 2). Similar observations were found for women. The observed HRs were as follows: 0.81 (95% CI: 0.66–0.99), 0.64 (95% CI: 0.54–0.74), and 0.37 (95% CI: 0.26–0.51), respectively.

When the HRs were estimated by cumulative DDD (≤90, 91–180, 181–364, and ≥365) using the lowest group as the reference group, the observed HRs were as follows: 0.96 (95% CI: 0.76–1.20), 1.01 (95% CI: 0.79–1.29), and 0.82 (95% CI: 0.67–1.00), respectively (Table 2).

In the stratum-specific analyses by groups of index years (2006–2008, 2009–2010, and 2011–2012), the observed HRs, as in the overall analysis, indicate an inverse association between fillings for antimuscarinic medications and lung cancer (Table S2).

Colon cancer

For colon cancer, the point estimates and 95% CIs for the overall HRs for the three different intervals for time since index date (<1 year, 1–4 years, and ≥4 years) were as follows: 0.91 (95% CI: 0.80–1.03), 0.81 (95% CI: 0.74–0.88), and 0.61 (95% CI: 0.51–0.73), respectively (Table 2). The observed estimated overall HRs were lower in the analyses where lag times were applied compared to the main analysis.

In the stratum-specific analyses by sex, all HRs for both men and women were <1. For men, the HRs in the different time intervals (<1 year, 1–4 years, and ≥4 years) were as follows: 0.94 (95% CI: 0.79–1.13), 0.81 (95% CI: 0.71–0.93), and 0.60 (95% CI: 0.46–0.78), respectively (Table 2). The observed estimates for women were 0.87 (95%

Table 2 HRs and 95% CIs for the end points, overall, by sex and cumulative DDD

	N	Unadjusted HR (95% CI)	Base adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]
Lung cancer				
Overall	9,053			
Unexposed	8,394	1 (reference)	1 (reference)	1 (reference)
Exposed	659			
<1 year	234	0.91 (0.79–1.04)	0.86 (0.76–0.99)	0.86 (0.75–0.98)
1–4 years	347	0.66 (0.59–0.74)	0.64 (0.57–0.71)	0.63 (0.56–0.70)
≥4 years	78	0.47 (0.37–0.59)	0.44 (0.35–0.55)	0.43 (0.34–0.55)
Sex				
Men	4,907			
Unexposed	4,571	1 (reference)	1 (reference)	1 (reference)
Exposed	336			
<1 year	128	0.92 (0.77–1.10)	0.89 (0.74–1.07)	0.90 (0.75–1.08)
1–4 years	168	0.63 (0.54–0.73)	0.61 (0.52–0.72)	0.62 (0.53–0.72)
≥4 years	40	0.52 (0.38–0.71)	0.50 (0.36–0.69)	0.51 (0.37–0.70)
Women	4,146			
Unexposed	3,823	1 (reference)	1 (reference)	1 (reference)
Exposed	323			
<1 year	106	0.92 (0.75–1.12)	0.83 (0.68–1.02)	0.81 (0.66–0.99)
1–4 years	179	0.72 (0.62–0.83)	0.66 (0.56–0.76)	0.64 (0.54–0.74)
≥4 years	38	0.42 0.31–0.59)	0.39 (0.28–0.54)	0.37 (0.26–0.51)
DDDs[c]				
≤90	340	1 (reference)	1 (reference)	1 (reference)
91–180	103	0.97 (0.77–1.21)	0.96 (0.76–1.20)	0.96 (0.76–1.20)
181–364	83	1.03 (0.81–1.32)	1.01 (0.79–1.28)	1.01 (0.79–1.29)
≥365	133	0.83 (0.68–1.02)	0.82 (0.67–1.00)	0.82 (0.67–1.00)
Colon cancer				
Overall	10,448			
Unexposed	9,537	1 (reference)	1 (reference)	1 (reference)
Exposed	911			
<1 year	263	0.96 (0.85–1.09)	0.91 (0.80–1.03)	0.91 (0.80–1.03)
1–4 years	508	0.86 (0.79–0.95)	0.81 (0.74–0.89)	0.81 (0.74–0.88)
≥4 years	140	0.64 (0.54–0.76)	0.61 (0.51–0.72)	0.61 (0.51–0.73)
Sex				
Men	5,556			
Unexposed	5,102	1 (reference)	1 (reference)	1 (reference)
Exposed	454			
<1 year	141	0.98 (0.82–1.16)	0.94 (0.80–1.12)	0.94 (0.79–1.13)
1–4 years	250	0.85 (0.75–0.97)	0.81 (0.71–0.93)	0.81 (0.71–0.93)
≥4 years	63	0.61 (0.47–0.79)	0.60 (0.46–0.78)	0.60 (0.46–0.78)
Women	4,892			
Unexposed	4,435	1 (reference)	1 (reference)	1 (reference)
Exposed	457			
<1 year	122	0.97 (0.80–1.17)	0.87 (0.72–1.05)	0.87 (0.72–1.05)
1–4 years	258	0.90 (0.79–1.02)	0.80 (0.70–0.91)	0.80 (0.70–0.91)
≥4 years	77	0.68 (0.54–0.86)	0.61 (0.49–0.78)	0.62 (0.49–0.78)
DDDs[c]				
≤90	472	1 (reference)	1 (reference)	1 (reference)
91–180	148	1.01 (0.84–1.22)	0.99 (0.82–1.20)	0.99 (0.82–1.20)
181–364	118	1.05 (0.86–1.29)	1.02 (0.83–1.25)	1.02 (0.83–1.25)
≥365	173	0.74 (0.62–0.89)	0.73 (0.61–0.87)	0.73 (0.61–0.87)

Notes: [a]Adjusted for the matching variables age, sex, and county of residence. [b]Adjusted for age, sex, and county of residence, income, education, and the smoking proxy variable. [c]Only including the exposed individuals.
Abbreviation: DDD, defined daily dose.

CI: 0.72–1.05), 0.80 (95% CI: 0.70–0.91), and 0.62 (95% CI: 0.49–0.78), respectively.

The observed estimated HRs for the different cumulative DDD groups (≤90, 91–180, 181–364, and ≥365), using the lowest group as the reference group, were as follows: 0.99 (95% CI: 0.82–1.20), 1.02 (95% CI: 0.83–1.25), and 0.73 (95% CI: 0.61–0.87), respectively.

An inverse association was observed between filling a prescription for antimuscarinic medications and colon cancer for all the three index year groups (Table S2).

Sensitivity analyses

The point estimates of the HRs in the sensitivity analyses for lung cancer and for colon cancer were <1 in all the time intervals (<1 year, 1–4 years, and ≥4 years) (Table S3). For lung cancer, the HRs were as follows: 0.84 (95% CI: 0.69–1.03), 0.70 (95% CI: 0.61–0.82), and 0.40 (95% CI: 0.28–0.47), respectively. The corresponding estimates for colon cancer were as follows: 0.92 (95% CI: 0.77–1.11), 0.90 (95% CI: 0.80–1.02), and 0.75 (95% CI: 0.59–0.95), respectively.

Discussion

Key findings

This study observed an inverse association between filling prescriptions for antimuscarinic medications and a diagnosis of lung cancer or colon cancer. Inverse associations confirm the result from the previous Danish study, investigating the same associations and estimating SIRs.[27] The inverse association was stronger with the longest follow-up time of at least 4 years. During the first year, there were in general no substantial differences between the two exposure groups and the risk of the cancers of interest. Inverse associations between both follow-up time >1 year and filling 365 DDDs or more and the cancers of interest were observed. This indicates that it is of no or small importance if the exposure is reported as time since treatment start or as cumulative DDDs. However, this association was more pronounced for colon cancer than for lung cancer. A possible dose–response association is consistent with results from a study based on Danish data.[27] The observed estimates were on similar levels for both men and women, in both cancer types, indicating that there is no sex-based difference in the association between filling prescriptions for antimuscarinic medications and the cancer end points of interest. Similarities in observed associations between men and women are consistent with the findings from Denmark.[27] The observed inverse associations are in accordance with previous findings from preclinical studies showing an inhibitory effect of antimuscarinic substances, blocking the M3-receptor, on cell proliferation and cancer cell growth in lung cancer and colon cancer cell lines.[22,24–26]

In the sensitivity analyses, inverse associations between exposure and lung or colon cancer were observed. The point estimates were on similar levels as observed in the main analyses, indicating no difference between the different antimuscarinic medications, demonstrating the robustness of our results.

Using no lag time for the main analysis was decided based on the preclinical studies reporting an inverse association. With an inverse association, there is no reason to suspect protopathic bias, the main reason for having a lag time.[45] However, when lag times were used, the point estimates decreased, indicating a stronger inverse association. The effect of lag times was most prominent during the first year of follow-up. Our observations of a decrease in the point estimates of the effect size with longer lag time confirm the results from a similar study investigating the association between proton pump inhibitors and gastric cancer.[45]

Only about 6% of the exposed individuals had a recorded diagnosis of OAB, which is likely explained by the fact that the majority of the diagnoses of OAB are given in primary care, which is not covered by the NPR. The overall higher prevalence of comorbid conditions among the exposed individuals could, to some extent, be due to surveillance bias.

The results of this study indicate a potential protective effect of antimuscarinic medications for OAB on lung cancer and colon cancer. However, further studies are required to confirm the results found in this study. The included study medications should possibly, in future studies, be studied regarding a potential cancer-protective effect.

Strengths

A major strength of this study is the use of the Swedish population-based registers with high validity and close to complete coverage of the entire Swedish population, which contributed to the quality of the study, the large sample size, and the generalizability of the results.[37,46,47]

The PDR records medications from filled prescriptions, which makes it more probable that the patient was actually exposed to the medication and eliminates the risk of recall bias regarding the exposure classification.[48] However, a filled prescription does not necessarily imply the use of a medication.

Limitations

One important limitation of this study is the lack of data on lifestyle factors such as smoking history and alcohol intake, well-known risk factors for cancer. However, the lack of information on smoking history was approached by using a diagnosis of COPD or a filled prescription for smoking cessation medication as a proxy for being a current or former smoker. However, this approach will most likely only have covered heavy smokers. The short follow-up time is also an important limitation of this study. As different cancer types have varying latency periods and the time from initiation to manifest malignancy is usually several years, ideally a long follow-up time is needed to make different assumptions about the risk of the outcome of interest and relevant exposure periods. Another possible limitation is the timing of the matching in relation to the application of exclusion criteria. The matching of unexposed individuals to the exposed individuals was done before exclusion. This lead to an uneven number of unexposed individuals matched to exposed individuals. However, this was done to avoid potential problems assigning index dates to the unexposed individuals since their index date was the same as the index date for the exposed individual they were matched to. Also, the inverse associations may to some extent be explained by the introduction of censoring due to filling a prescription of a non-tablet formulation of the study medication and as censoring only applied to the exposed individuals. It should, however, be noted that few individuals filled prescriptions for non-tablet formulations.

Conclusion

An inverse association between exposure to antimuscarinic medications, used in the treatment of OAB, and a diagnosis of colon cancer or lung cancer was observed. However, it is important to consider the relatively short follow-up time.

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Author contributions

LL performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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Supplementary materials

Table S1 ATC codes used to identify medications in the PDR used as disease proxies

Diseases	ATC codes
Hypertension	C02, C03, C07AA01-C07AA06, C07AA08, C07AA27, C07AB, C07Ag, C08, and C09
Diabetes mellitus	A10
Obesity	A09

Abbreviation: ATC, Anatomic Therapeutic Chemical classification system; PDR, Prescribed Drug Register.

Table S2 HR and 95% CIs for the end points, overall using 6-month and 12-month lag time, and by inclusion year using no lag time

Lung cancer				
	n	**Unadjusted HR (95% CI)**	**Base adjusted HR (95% CI)[a]**	**Fully adjusted HR (95% CI)[b]**
6-month lag time				
Overall	7,756			
Unexposed	7,226	1 (reference)	1 (reference)	1 (reference)
Exposed	530			
<1 year	176	0.74 (0.63–0.88)	0.70 (0.60–0.82)	0.70 (0.60–0.82)
1–4 years	311	0.68 (0.61–0.76)	0.65 (0.58–0.73)	0.64 (0.57–0.72)
≥4 years	43	0.36 (0.26–0.48)	0.33 (0.24–0.45)	0.33 (0.24–0.45)
12-month lag time				
Overall	6,532			
Unexposed	6,107	1 (reference)	1 (reference)	1 (reference)
Exposed	425			
<1 year	139	0.64 (0.54–0.76)	0.62 (0.52–0.74)	0.62 (0.52–0.74)
1–4 years	258	0.66 (0.58–0.75)	0.63 (0.55–0.71)	0.61 (0.54–0.70)
≥4 years	28	0.34 (0.23–0.50)	0.31 (0.21–0.46)	0.30 (0.21–0.45)
Index year				
2006–2008	5,663			
Unexposed	5,237	1 (reference)	1 (reference)	1 (reference)
Exposed	426			
<1 year	103	0.81 (0.66–0.99)	0.78 (0.63–0.95)	0.77 (0.62–0.94)
1–4 years	245	0.78 (0.68–0.89)	0.75 (0.66–0.86)	0.75 (0.66–0.86)
≥4 years	78	0.50 (0.40–0.63)	0.47 (0.37–0.60)	0.47 (0.37–0.59)
2009–2010	2,345			
Unexposed	2,181	1 (reference)	1 (reference)	1 (reference)
Exposed	164			
<1 year	74	1.02 (0.80–1.30)	0.97 (0.76–1.23)	0.97 (0.76–1.24)
1–4 years	90	0.56 (0.45–0.69)	0.53 (0.43–0.65)	0.51 (0.41–0.63)
≥4 years	0	–	–	–
2011–2012	1,045			
Unexposed	976	1 (reference)	1 (reference)	1 (reference)
Exposed	69			
<1 year	57	0.97 (0.74–1.28)	0.92 (0.70–1.21)	0.91 (0.69–1.20)
1–4 years	12	0.24 (0.14–0.43)	0.24 (0.14–0.42)	0.23 (0.13–0.42)
≥4 years	0	–	–	–
Colon cancer				
	n	**Unadjusted HR (95% CI)**	**Base adjusted HR (95% CI)[a]**	**Fully adjusted HR (95% CI)[b]**
6-month lag time				
Overall	9,094			
Unexposed	8,315	1 (reference)	1 (reference)	1 (reference)
Exposed	779			
<1 year	242	0.92 (0.80–1.05)	0.86 (0.75–0.98)	0.86 (0.75–0.98)
1–4 years	449	0.86 (0.78–0.95)	0.81 (0.73–0.89)	0.81 (0.73–0.89)
≥4 years	88	0.57 (0.46–0.70)	0.53 (0.43–0.66)	0.53 (0.43–0.66)

(*Continued*)

Table S2 (*Continued*)

Colon cancer				
	n	**Unadjusted HR (95% CI)**	**Base adjusted HR (95% CI)[a]**	**Fully adjusted HR (95% CI)[b]**
12-month lag time				
Overall	7,768			
Unexposed	7,120	1 (reference)	1 (reference)	1 (reference)
Exposed	648			
<1 year	210	0.87 (0.76–1.01)	0.81 (0.70–0.93)	0.81 (0.71–0.94)
1–4 years	392	0.86 (0.77–0.95)	0.81 (0.73–0.90)	0.80 (0.72–0.89)
≥4 years	46	0.43 (0.32–0.58)	0.40 (0.30–0.54)	0.40 (0.30–0.54)
Index year				
2006–2008	6,421			
Unexposed	5,818	1 (reference)	1 (reference)	1 (reference)
Exposed	603			
<1 year	109	0.81 (0.67–0.99)	0.78 (0.64–0.95)	0.78 (0.64–0.96)
1–4 years	354	1.08 (0.96–1.20)	1.01 (0.91–1.14)	1.01 (0.90–1.13)
≥4 years	140	0.70 (0.59–0.83)	0.66 (0.55–0.79)	0.66 (0.56–0.79)
2009–2010	2,796			
Unexposed	2,573	1 (reference)	1 (reference)	1 (reference)
Exposed	223			
<1 year	95	1.27 (1.03–1.58)	1.18 (0.95–1.47)	1.18 (0.95–1.46)
1–4 years	128	0.65 (0.54–0.78)	0.61 (0.51–0.73)	0.60 (0.50–0.73)
≥4 years	0	–	–	–
2011–2012	1,231			
Unexposed	1,146	1 (reference)	1 (reference)	1 (reference)
Exposed	85			
<1 year	59	0.91 (0.69–1.19)	0.84 (0.64–1.10)	0.85 (0.65–1.11)
1–4 years	26	0.42 (0.28–0.62)	0.39 (0.26–0.58)	0.39 (0.26–0.58)
≥4 years	0	–	–	–

Notes: [a]Adjusted for the matching variables age, sex, and county of residence. [b]Adjusted for age, sex, and county of residence, income, education, and the smoking proxy variable.

Table S3 HR and 95% CIs for the end points for tolterodine

	n	**Unadjusted HR (95% CI)**	**Base adjusted HR (95% CI)[a]**	**Fully adjusted HR (95% CI)[b]**
Lung cancer				
Unexposed	4,423	1 (reference)	1 (reference)	1 (reference)
Exposed	348			
<1 year	109	0.88 (0.72–1.07)	0.84 (0.69–1.03)	0.84 (0.69–1.03)
1–4 years	196	0.72 (0.62–0.83)	0.71 (0.61–0.82)	0.70 (0.61–0.82)
≥4 years	43	0.43 (0.30–0.60)	0.41 (0.29–0.58)	0.40 (0.28–0.57)
Colon cancer				
Unexposed	5,126	1 (reference)	1 (reference)	1 (reference)
Exposed	512			
<1 year	130	0.97 (0.81–1.17)	0.92 (0.77–1.11)	0.92 (0.77–1.11)
1–4 years	294	0.95 (0.84–1.07)	0.90 (0.80–1.02)	0.90 (0.80–1.02)
≥4 years	88	0.74 (0.59–0.94)	0.75 (0.59–0.95)	0.75 (0.59–0.95)

Notes: [a]Adjusted for the matching variables age, sex, and county of residence. [b]Adjusted for age, sex, and county of residence, income, education, and the smoking proxy variable.