Title: Exposure to ranitidine and risk of bladder cancer: a nested case-control study.

Short title: Ranitidine and bladder cancer risk

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HIGHLIGHTS

WHAT IS KNOWN

- Ranitidine has been widely used for various indications including gastroesophageal reflux disease and peptic ulcers.
- Ranitidine has recently been shown to contain the carcinogen N-nitrosodimethylamine and increase urinary N-nitrosodimethylamine.
- Few epidemiological studies have investigated the specific association between ranitidine use and bladder cancer risk.

WHAT IS NEW HERE

- Use of ranitidine was associated with increased bladder cancer risk but use of proton pump inhibitors, which have similar indications, was not associated with bladder cancer risk.
- Additional studies are required to attempt to replicate this finding in other settings.

Background

Ranitidine has been shown to contain the carcinogen N-nitrosodimethylamine and increase urinary N-nitrosodimethylamine in humans. We investigated whether ranitidine use is associated with increased bladder cancer risk.

Methods

A nested case-control study was conducted within the Primary Care Clinical Informatics Unit Research database which contains general practice (GP) records from Scotland. Bladder cancer cases, diagnosed between 1999 and 2011, were identified and matched with up to five controls (based on age, gender, GP practice and date of registration). Ranitidine, other histamine-2 receptor agonists and proton pump inhibitors were identified from prescribing records. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression after adjusting for comorbidities and smoking.

Results

There were 3,260 cases and 14,037 controls. There was evidence of an increased risk of bladder cancer in ranitidine users, compared with non-users, (fully adjusted OR= 1.22 95% CI 1.06, 1.40) which was more marked with use for over 3 years of ranitidine (fully adjusted OR=1.43 95% CI 1.05,1.94). In contrast, there was little evidence of any association between proton pump inhibitor use and bladder cancer risk based upon any use (fully adjusted OR=0.98 95% CI 0.88, 1.11) or over 3 years of use (fully adjusted OR=0.98 95% CI 0.80, 1.20).

Conclusion

In this large population-based study, the use of ranitidine particularly long-term use was associated with an increased risk of bladder cancer. Further studies are necessary to attempt to replicate this finding in other settings.

Keywords:

Ranitidine, Dimethylnitrosamine, Proton-pump inhibitor, Bladder cancer, Epidemiology.

Introduction

N-nitrosodimethylamine (NDMA) is a nitrosamine impurity which is known to be carcinogenic in animals[1, 2]. NDMA has been classified by the International Agency for Research on Cancer as "probably carcinogenic to humans" group 2A[2]. NDMA has been implicated in the induction of cancer at a number of sites, including bladder cancer, and it is thought to be involved in the increased risk of bladder cancer observed in patients with Schistosoma infection[3].

Ranitidine is a histamine-2 receptor agonist used for various indications including gastroesophageal reflux disease and peptic ulcers. Ranitidine is commonly used worldwide and is available on prescription and over-the-counter. For instance, in the United States it was one of the top 50 most commonly prescribed medicines in 2018[4] and in England, over 6 million prescriptions were issued in 2019[5]. In 2016, an in-vitro study showed that NDMA could be created by ranitidine at a range of pH levels to simulate gastric conditions[3]. The same study also investigated healthy volunteers (aged 20 to 49 years) and showed that 24 hour urinary NDMA was increased 400 fold, and N-nitrosamines 5 fold, after ranitidine consumption[3]. In 2019 the United States Food and Drug Administration first recalled some ranitidine medicines because they contained NDMA and in 2020 recalled all ranitidine products[6-8], and other regulatory bodies conducted similar recalls[8]. The source of the NDMA in ranitidine is unclear but it could result from contaminated material in the manufacturing process of ranitidine[6], or from storage conditions[8, 9]. Alternatively, it has been suggested that ranitidine is inherently unstable[7] and capable of creating NDMA from an intermediate or from ranitidine itself[3, 6, 7]. Despite these concerns, an epidemiological study has not had the specific aim to investigate ranitidine and

bladder cancer risk. One previous study[10] reported limited evidence of an increased risk of bladder cancer with combined ranitidine or cimetidine use (relative risk= 1.58; 95% CI 0.93, 2.69). Two recent studies[11, 12] investigating ranitidine and risk of any cancer reported bladder cancer risk as a secondary outcome, but power was limited as relatively small numbers of ranitidine users developed bladder cancer in these studies (16[11] and 118[12]).

We recently reported the results of a hypothesis-generating screening study[13] within a Scottish primary care dataset (the Primary Care Clinical Information Unit Research (PCCIUR) database[14]) in which we observed an increased risk of bladder cancer in ranitidine users. However, our hypothesis-generating screening study did not quantify ranitidine use on the basis of quantity or strength, adjust for confounders relevant to ranitidine use, investigate histamine-2 receptor agonists as a class or compare ranitidine to proton pump inhibitors as has been recommended[3]. Consequently, we have conducted more extensive analyses to investigate whether ranitidine increases bladder cancer risk within the PCCIUR dataset.

Methods

Data source

Data for this study was obtained from Primary Care Clinical Information Unit Research (PCCIUR) database[14] which captured General Practice records for over two million patients registered at 393 general practices in Scotland between 1993 and 2011. The PCCIUR data contains demographics, diagnoses, prescriptions and lifestyle characteristics (including smoking and alcohol intake) and has been widely used in epidemiological research[15-18]. Data access was approved by the Research

Applications and Data Management Team of the University of Aberdeen, and we obtained ethics approval for this analysis from the School of Medicine, Dentistry and Biomedical Sciences Research Ethics Committee at Queen's University Belfast (reference number: 18.02v2). All authors had access to the study data and reviewed and approved the final manuscript.

Study design

A nested case-control study was conducted within the PCCIUR database. Cases were identified based upon a primary care record of a diagnosis of primary bladder cancer (read code B49) between 1999 and 2011. Cases were excluded if they had a cancer diagnosis, excluding non-melanoma skin cancer, before their bladder cancer diagnosis. Cases were excluded if they had a record of other different cancers diagnosed on the same date as their bladder cancer. Up to five controls were matched to each case on practice, year of birth (plus or minus five years), gender and year of registration (in categories). The index date was defined as the date of the bladder cancer diagnosis within the case and this index date was allocated to all controls within the matched set of the case. Controls were required to be alive, registered with their GP and free from cancer (with the exception of non-melanoma skin cancer) on the index date. Cases and controls were required to have at least three years of primary care records with the same general practice before the index date.

Within each matched set, the exposure period, i.e. the period of time over which medicine use was determined, began on either 1 January 1993 (as prescriptions before this time were less likely to be electronically recorded), or the most recent GP

registration date if this occurred after January 1993. This ensured that the exposure period was the same duration for all members of each matched set. The exposure period ended one year before the index date, to reduce the risk of reverse causality and exclude medications that are unlikely to have had sufficient time to cause cancer.

Exposure

Medication use was determined from primary care records of each individual prescription made in the exposure period. For each case and control, we extracted prescriptions for oral ranitidine and other histamine-2 receptor antagonists (including cimetidine, famotidine and nizatidine) and oral proton pump inhibitors (including esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole sodium). A pack size of 28 was allocated where the quantity was missing or assumed incorrect (less than 0.1% of prescriptions) and the most commonly used dose, by medication, was allocated where the dose was missing (less than 0.1% of prescriptions). For instance, for ranitidine a dose of 150mg was assumed when dose was missing. Defined daily doses (DDD) were calculated from the quantity of tablets and dose, as defined by World Health Organization.

Covariates

Comorbidities were identified from primary care diagnoses based upon read codes prior to the index date (excluding the year before the index date). Diagnoses were identified of relevance to the outcome (including urinary tract infections and/or cystitis) and exposure (including gastro-oesophageal reflux disease, Barrett's oesophagus, and peptic ulcer). Additionally the following separate conditions were

identified taken from those included in the Charlson Comorbidity index and based upon published code lists[19]: diabetes, myocardial infarction, coronary heart disease, heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic obstructive pulmonary disease, osteoporosis, severe mental illness, rheumatological disease, renal disease, liver disease, irritable bowel disease, human immunodeficiency viruses (HIV) and hemiplegia/paraplegia. Smoking status (non-smoker, ex-smoker, current smoker) and alcohol consumption (none, low [e.g. moderate or light drinker], or high intake [e.g. above recommended limits, chronic alcoholism]), were determined from the record indicating the highest smoking or alcohol category prior to the index date (excluding the year before the index date). Celecoxib use was determined from prescription records. The Townsend score based upon postcode of the GP practice was determined as a measure of deprivation[20].

Statistical analysis

The characteristics of cases and controls were compared using descriptive statistics (for continuous variables) or frequencies and percentages (for categorical variables). Conditional logistic regression was initially used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between ranitidine and bladder cancer. The matched design accounted for GP practice, gender, year of registration and age in categories, and age in years was entered into all models. The model for the main analysis included: gastro-oesophageal reflux disease, Barrett's oesophagus, peptic ulcer, urinary tract infections/cystitis, the Charlson comorbidities (mentioned above) and celecoxib use. A separate evaluation was conducted additionally adjusting for smoking (based upon a complete-case analysis). Analyses

were repeated by DDDs and number of prescriptions. Similar analyses were conducted for other histamine-2 receptor agonists (excluding ranitidine), cimetidine and for proton pump inhibitors.

Sensitivity analyses

Various additional analyses were conducted, including two active comparator analyses. The first compared ranitidine users with non-users of ranitidine who used other histamine-2 receptor agonists to investigate the specificity of any association to ranitidine. The second compared ranitidine users to non-users of ranitidine who used proton pump inhibitors to attempt to reduce confounding by indication as previously suggested[3]. A separate analysis was conducted additionally adjusting for alcohol intake (based upon complete cases). A further sensitivity analysis was conducted adjusting for smoking using multiple imputation with chained equations[21] to account for missing smoking data. First, an imputation model was created using ordered logit models including ranitidine, age, year, gender and comorbidities and case status. Twenty-five imputations were conducted and results were combined using Rubin's rules[21]. This imputation approach was repeated for alcohol. An analysis was conducted adjusting for smoking using the categories: non-smoker, ex-smoker, current smoker and current heavy smoker (based upon a read code indicating smoking more than 20 cigarettes per day). A separate analysis was conducted not adjusting for potential indications for ranitidine to avoid the risk of over-adjustment (i.e.removing gastro-oesophageal reflux disease, Barrett's oesophagus, peptic ulcer from the model) and. Finally, the duration of the lag was increased to remove prescriptions in the two year period prior to the index date to further reduce any potential for reverse causation.

The study was approved by the Research Applications and Data Management Team at the University of Aberdeen and Queen's University Belfast School of Medicine Ethics Committee (reference number: 18.02v2). All statistical analyses were conducted using STATA 16 (StataCorp, College Station, TX, USA).

Results

Characteristics of cases and controls

Overall, 3,260 bladder cancer cases and 14,037 controls were identified and met the inclusion criteria. The majority of cases (2665; 82%) had 4 or more matched controls. The median exposure period within each matched set was 8.4 years (interquartile range 5.7 to 11.1). Characteristics of the cases and controls are summarised in Table 1. The median age at diagnosis of bladder cancer was 72 years (interquartile range 64 to 79) and 29% (957) were female. A greater proportion of cases compared with controls were former (26.1% vs 21.0%) or current smokers (28.9% vs 22.4%), but alcohol intake appeared similar. Comorbidities were generally similar between cases and controls with the largest differences seen for coronary heart disease (22.2% vs 18.2%), urinary tract infections/cystitis (8.9% vs 5.6%), chronic obstructive pulmonary disease (11.6% vs 8.4%) and peptic ulcers (8.9% vs 5.6%).

Associations between ranitidine and bladder cancer

Results from the main analyses are shown in Table 2. Overall, 14.0% of cases and 10.9% of controls used ranitidine. There was some evidence of an increased risk of bladder cancer in ranitidine users (OR=1.28 95% CI 1.14, 1.44) which remained after

adjustment for confounders (fully adjusted OR=1.22 95% CI 1.06, 1.40). The associations appeared stronger with greater use based upon either DDDs or prescriptions. For instance, in participants using more than 1095 ranitidine DDDs the fully adjusted OR was 1.43 (95% CI 1.05, 1.94), compared with no use. The association between non-ranitidine histamine-2 receptor agonists and bladder cancer risk was generally similar particularly for use of over 1095 DDDs (fully adjusted OR=1.33 95% CI 0.83, 2.15), compared with no use. There was little evidence of any association between proton pump inhibitor use and bladder cancer risk based upon any use (fully adjusted OR=0.98 95% CI 0.88, 1.11) or use of over 1095 DDDs (fully adjusted OR=0.98 95% CI 0.80, 1.20).

Sensitivity analyses

Sensitivity analyses are shown in Table 3. Associations were similar after removing prescriptions in the 2 years before diagnosis, when adjusting for smoking frequency, when additionally adjusting for alcohol, or when adjusting for alcohol and smoking using multiple imputation. The association was largely attenuated when comparing ranitidine users to ranitidine non-users who used other histamine-2 receptor agonists (adjusted OR=1.05 95% CI 0.86, 1.28), but remained when comparing ranitidine users to ranitidine non-users who used proton pump inhibitors (adjusted OR=1.20 95% CI 1.04, 1.39).

Discussion

In our analysis, we observed a 22% increased risk of bladder cancer in ranitidine users, which increased to 43% in participants using more than 3 years of ranitidine (1095 DDDs), compared with non-users. There was no association between use of

proton pump inhibitors and bladder cancer risk and, importantly, ranitidine users also had a marked increase in bladder cancer risk when compared with users of proton pump inhibitors. In contrast, there was some weak evidence of an association between non-ranitidine histamine-2 receptor agonists and bladder cancer risk but there was little evidence of difference in bladder cancer risk when directly comparing ranitidine users to users of non-ranitidine histamine-2 receptor agonists.

Few previous studies have investigated ranitidine and bladder cancer risk and our findings are generally consistent with these studies. One study[10] did not focus on ranitidine alone but did show limited evidence of an increase in the risk of bladder cancer (relative risk= 1.58; 95% CI 0.93, 2.69) in users of ranitidine or cimetidine. A recent UK study[11] observed an increased bladder cancer risk in ranitidine users of 22% (hazard ratio=1.22 95% CI 0.74, 2.01) compared with non-users, and of 30% (hazard ratio=1.30 95% CI 0.69, 2.46) compared with omeprazole users, but had limited power. A recent South Korean study[12] observed an increase in bladder cancer risk of 41% (hazard ratio=1.41 95% CI 0.88, 2.24) in ranitidine users compared with famotidine users.

The cause of the increased risk of bladder cancer in ranitidine users is unclear. The increased risk in bladder cancer amongst ranitidine users is consistent with concerns that ranitidine use can lead to exposure to NDMA[3, 6, 7] and that extended exposure to ranitidine, particularly as it increases urinary NDMA, could increase bladder cancer risk[3]. However, there is some debate over whether the levels of NDMA detected within ranitidine are sufficiently high to increase cancer risk[7]. Also, it is worth noting that ranitidine investigated in our study was prescribed before 2011, many years

before evidence that ranitidine increased NDMA exposure emerged[3, 6, 7]. Regardless, these findings merit further investigation in epidemiological studies to examine the association between both ranitidine and other histamine-2 receptor agonists across a range of settings. Should this association be replicated, patients and clinicians should incorporate this association into their consideration of risks and benefits of ranitidine particularly when alternative treatments such as proton pump inhibitors are available. It is worth noting that even if a medication increased bladder cancer risk by 20%, because bladder cancer is uncommon (in Scotland around 15 per 100,000 person years[22]), the number needed to harm would be around 33,000 after 1 year. Also, the population attributable fraction, assuming the medication was used by 10% of the population, would be around 2%. Additionally, further studies could investigate the hypothesis that use of ascorbic acid with ranitidine could markedly reduce NDMA formation, as ascorbic acid rapidly scavenges nitrite[23].

Our study has several strengths. The PCCIUR is a population-based primary care database. Prescription records, of up to 18 years, were used to identify medication use eliminating the potential for recall bias. We had access to a wide range of confounders including smoking and alcohol use. Although we did not have data on the specific reason for ranitidine use, we demonstrated that the association with bladder cancer risk remained when comparing ranitidine users with proton pump inhibitors who would have similar indications and share many risk factors. In contrast, the associations were attenuated when comparing ranitidine users to users of other histamine-2 receptor agonists suggesting a reduction in power, a class effect of histamine-2 receptor agonists or that the association could be explained by confounding by indications for histamine-2 receptor agonists.

A weakness of our study is that we would have missed intravenous ranitidine and over-the-counter ranitidine. However, ranitidine is only available over-the counter in the UK for short term use (less than 2 weeks), at low doses (75mg) and for limited indications (short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity)[24]. Also, available data suggest that UK over-the-counter purchases account for only around 10% of ranitidine packs supplied, based upon data from Wales in 2012[25]. Furthermore, methodological studies have shown prescribing data can give valid estimates even though drugs are available over-the-counter[26]. Another weakness is compliance as patients prescribed ranitidine may not have taken it, however this seems less of an issue for longer term users. Primary care records were used to identify bladder cancer but a recent study showed that 97% of bladder cancer cases identified in primary care records were confirmed from linkage to cancer registry data, hospital records or medical review[27]. We did not have access to the stage or grade of the bladder cancer diagnosis to allow investigation of high risk disease. There remains the risk of Type 1 error and the observed association is not independent from the association seen in our screening study[13], however our re-analyses, as recommended to better understand associations[28], has allowed us to better quantify ranitidine exposure, better adjust for confounders, investigate drugs in classes, and conduct active compactor analyses (e.g. comparing ranitidine to proton pump inhibitors). We were unable to determine the indication for ranitidine use, but similar results were observed when comparing ranitidine users to PPI users who are likely to have similar indications. We were unable to control for several bladder cancer risk factors such as family history and occupational exposures (particularly workers in the metal, tobacco, rubber and dye industries thought to be caused by

exposure to various carcinogens[29]). Finally, smoking and alcohol were incomplete and did not capture detailed information on the extent of exposure, and consequently there remains the possibility of residual confounding.

Conclusion

In this large population-based study, the use of ranitidine particularly long-term use was associated with an increased risk of bladder cancer. Further studies are necessary to attempt to replicate this finding.

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466 Table 1. Characteristics of bladder cancer cases and controls.

		Cases	Controls	P[a]
Year of diagnosis/index date:	1990-99	196 (6.0%)	881 (6.3%)	Matched
	2000-03	984 (30.2%)	4125 (29.4%)	
	2004-07	1446 (44.4%)	6228 (44.4%)	
	2008-11	634 (19.4%)	2803 (20.0%)	
Age at diagnosis/index date:	<50	122 (3.7%)	830 (5.9%)	Matched
	40-59	328 (10.1%)	2115 (15.1%)	
	60-69	922 (28.3%)	4217 (30.0%)	
	70-79	1158 (35.5%)	4475 (31.9%)	
	≥ 80	730 (22.4%)	2400 (17.1%)	
Gender: Female		957 (29.4%)	4187 (29.8%)	Matched
Deprivation: 1st fifth (least deprived)		846 (26.0%)	3597 (25.6%)	Matched
2nd fifth		781 (24.0%)	3334 (23.8%)	
3rd fifth		544 (16.7%)	2362 (16.8%)	
4th fifth		657 (20.2%)	2847 (20.3%)	
5th fifth (most deprived)		427 (13.1%)	1877 (13.4%)	
Missing		5 (0.2%)	20 (0.1%)	
Smoking status: Never		799 (24.5%)	4601 (32.8%)	<0.001
Former		850 (26.1%)	2943 (21.0%)	
Current		943 (28.9%)	3139 (22.4%)	
Missing		668 (20.5%)	3354 (23.9%)	
Alcohol intake: None		496 (15.2%)	1861 (13.3%)	0.98
Low		1635 (50.2%)	6791 (48.4%)	
High		124 (3.8%)	551 (3.9%)	
Missing		1005 (30.8%)	4834 (34.4%)	
Selected comorbidities				
Gastro-oesophageal reflux disease		189 (5.8%)	667 (4.8%)	0.06
Barrett's oesophagus		24 (0.7%)	63 (0.4%)	0.15
Peptic ulcer		406 (12.5%)	1328 (9.5%)	<0.001
Urinary tract infections/cystitis		290 (8.9%)	790 (5.6%)	<0.001
Diabetes		368 (11.3%)	1257 (9.0%)	<0.001
Myocardial infarction		304 (9.3%)	1118 (8.0%)	0.13
Coronary heart disease		725 (22.2%)	2554 (18.2%)	0.001
Heart failure		148 (4.5%)	521 (3.7%)	0.56
Peripheral vascular disease		242 (7.4%)	715 (5.1%)	<0001
Dementia		42 (1.3%)	222 (1.6%)	<0.001
Cerebrovascular disease		314 (9.6%)	1150 (8.2%)	0.48
Chronic obstructive pulmonary disease		378 (11.6%)	1180 (8.4%)	<0.001
Osteoporosis		80 (2.5%)	337 (2.4%)	0.63
Severe mental illness		676 (20.7%)	2940 (20.9%)	0.58
Rheumatological disease		69 (2.1%)	338 (2.4%)	0.17
Renal disease		198 (6.1%)	570 (4.1%)	0.003
Liver disease		23 (0.7%)	99 (0.7%)	0.69
Irritable bowel disease		175 (5.4%)	653 (4.7%)	0.04
Celecoxib use		147 (4.5%)	453 (3.2%)	0.001

467 [a]P-value from conditional logistic regression accounting for matching and adjusting for age.

Table 2. Association between ranitidine, other histamine-2 receptor agonists, proton pump inhibitors and bladder cancer risk.

Medication	Cases	Controls	Age adjusted OR[a] (95% CI)	P (trend)	Adjusted[a] OR (95% CI)	P (trend)	Fully adjusted[b] OR (95% CI)	P (trend)
Ranitidine								
None	2805 (86.0%)	12508 (89.1%)	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
User	455 (14.0%)	1529 (10.9%)	1.28 (1.14, 1.44)	<0.001	1.20 (1.06, 1.36)	0.003	1.22 (1.06, 1.40)	0.005
1-182 DDDs	214 (6.6%)	758 (5.4%)	1.24 (1.05, 1.45)	0.011	1.17 (0.99, 1.38)	0.06	1.18 (0.98, 1.42)	0.087
182-365 DDDs	58 (1.8%)	208 (1.5%)	1.15 (0.85, 1.56)	0.369	1.08 (0.79, 1.47)	0.624	1.24 (0.85, 1.79)	0.264
365-1095 DDDs	106 (3.3%)	347 (2.5%)	1.30 (1.04, 1.64)	0.024	1.20 (0.95, 1.51)	0.132	1.17 (0.89, 1.54)	0.269
>1095 DDDs	77 (2.4%)	216 (1.5%)	1.54 (1.17, 2.04)	0.002 (<0.001)	1.45 (1.09, 1.93)	0.01 (0.002)	1.43 (1.05, 1.94)	0.021 (0.004)
1-6 prescriptions	229 (7.0%)	797 (5.7%)	1.25 (1.07, 1.47)	0.005	1.19 (1.01, 1.39)	0.037	1.17 (0.98, 1.41)	0.091
7-12 prescriptions	58 (1.8%)	246 (1.8%)	1.01 (0.75, 1.36)	0.965	0.97 (0.71, 1.31)	0.833	1.19 (0.84, 1.69)	0.318
13-36 prescriptions	110 (3.4%)	334 (2.4%)	1.35 (1.07, 1.70)	0.01	1.23 (0.97, 1.55)	0.086	1.25 (0.95, 1.63)	0.107
>36 prescriptions	58 (1.8%)	152 (1.1%)	1.76 (1.27, 2.42)	0.001 (<0.001)	1.65 (1.19, 2.29)	0.003 (0.001)	1.44 (1.01, 2.04)	0.042 (0.003)
Other histamine-2 receptor agonists (excluding ranitidine)								
None	3006 (92.2%)	13114(93.4%)	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
User	254 (7.8%)	923(6.6%)	1.16 (0.99, 1.35)	0.061	1.07 (0.91, 1.25)	0.4	1.04 (0.87, 1.24)	0.667
1-182 DDDs	139 (4.3%)	538 (3.8%)	1.09 (0.90, 1.34)	0.373	1.02 (0.84, 1.25)	0.831	0.95 (0.75, 1.19)	0.637
182-365 DDDs	36 (1.1%)	128 (0.9%)	1.22 (0.83, 1.80)	0.307	1.10 (0.74, 1.62)	0.636	0.89 (0.55, 1.45)	0.638
365-1095 DDDs	51 (1.6%)	169 (1.2%)	1.20 (0.86, 1.67)	0.285	1.09 (0.78, 1.53)	0.608	1.35 (0.91, 2.00)	0.137
>1095 DDDs	28 (0.9%)	88 (0.6%)	1.36 (0.87, 2.12)	0.176 (0.04)	1.28 (0.81, 2.00)	0.288 (0.244)	1.33 (0.83, 2.15)	0.239 (0.191)
Cimetidine								
Non-user	3026(92.8%)	13178(93.9%)	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
User	234(7.2%)	859(6.1%)	1.15 (0.98, 1.34)	0.088	1.06 (0.90, 1.25)	0.477	1.02 (0.85, 1.23)	0.845
Proton pump inhibitors								
None	2437(74.8%)	10881 (77.5%)	1.00 (ref. cat.)		1.00 (ref. cat.)		1.00 (ref. cat.)	
User	823(25.2%)	3156 (22.5%)	1.13 (1.02, 1.24)	0.015	1.01 (0.91, 1.12)	0.813	0.98 (0.88, 1.11)	0.79
1-182 DDDs	338 (10.4%)	1351 (9.6%)	1.13 (0.98, 1.29)	0.084	1.05 (0.92, 1.21)	0.481	1.00 (0.86, 1.17)	0.962
182-365 DDDs	91 (2.8%)	356 (2.5%)	1.14 (0.89, 1.45)	0.292	1.03 (0.80, 1.32)	0.826	1.02 (0.77, 1.34)	0.912
365-1095 DDDs	188 (5.8%)	736 (5.2%)	1.03 (0.87, 1.23)	0.712	0.93 (0.78, 1.12)	0.465	0.93 (0.76, 1.14)	0.5
>1095 DDDs	206 (6.3%)	713 (5.1%)	1.22 (1.03, 1.45)	0.021 (0.024)	1.01 (0.84, 1.22)	0.877 (0.860)	0.98 (0.80, 1.20)	0.863 (0.666)

Abbreviations: DDDs, Daily Defined Doses; OR, Odds Ratio.

[a]Model contains age, gastro-oesophageal reflux disease, Barrett's oesophagus, peptic ulcer, urinary tract infections/cystitis and charlson comorbidities (diabetes, myocardial infarction, coronary heart disease, heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic obstructive pulmonary disease, osteoporosis, severe mental illness, rheumatological disease, renal disease, liver disease, irritable bowel disease, human immunodeficiency viruses) and celecoxib use.
[b]Model contains all variables in and smoking status.

Table 3. Sensitivity analyses for the association between ranitidine and bladder cancer risk.

Medication	Cases *n*	Controls *n*	Adjusted[a] OR (95%CI)				
			User vs. non-user	1-182 DDDs vs. non-user	182-365 DDDs vs. non-user	365-1095 DDDs vs. non-user	>1095 DDDs vs. non-user
Main analysis	3260	14037	1.20 (1.06, 1.36)	1.17 (0.99, 1.38)	1.08 (0.79, 1.47)	1.20 (0.95, 1.51)	1.45 (1.09, 1.93)
Removing prescriptions in the 2 year before the index date	3260	14037	1.23 (1.08, 1.39)	1.26 (1.07, 1.49)	1.00 (0.72, 1.40)	1.26 (0.98, 1.62)	1.29 (0.94, 1.77)
Comparing ranitidine users to users of other histamine-2 receptor agonists							
Unadjusted	650	2229	1.04 (0.86, 1.27)	1.01 (0.80, 1.27)	0.94 (0.66, 1.33)	1.06 (0.80, 1.41)	1.26 (0.91, 1.73)
Adjusted	650	2229	1.05 (0.86, 1.28)	1.02 (0.81, 1.28)	0.94 (0.66, 1.33)	1.05 (0.79, 1.39)	1.27 (0.91, 1.75)
Comparing ranitidine users to users of proton pump inhibitors							
Unadjusted	1048	3892	1.18 (1.02, 1.37)	1.14 (0.95, 1.37)	1.06 (0.77, 1.46)	1.20 (0.94, 1.54)	1.43 (1.07, 1.91)
Adjusted	1048	3892	1.20 (1.04, 1.39)	1.17 (0.97, 1.41)	1.08 (0.78, 1.49)	1.20 (0.93, 1.53)	1.45 (1.08, 1.94)
Adjusting for smoking (multiple imputation)	3260	14037	1.20 (1.06, 1.36)	1.17 (0.99, 1.39)	1.12 (0.82, 1.53)	1.17 (0.93, 1.48)	1.45 (1.09, 1.92)
Adjusting for smoking frequency[b] (complete case)	2525	9175	1.22 (1.06, 1.40)	1.18 (0.98, 1.42)	1.23 (0.85, 1.79)	1.17 (0.89, 1.54)	1.43 (1.06, 1.95)
Adjusting for alcohol intake (complete case)	2162	7164	1.25 (1.08, 1.45)	1.20 (0.98, 1.47)	1.30 (0.87, 1.93)	1.20 (0.90, 1.60)	1.48 (1.06, 2.06)
Adjusting for alcohol intake (multiple imputation)	3260	14037	1.20 (1.06, 1.36)	1.17 (0.99, 1.38)	1.08 (0.79, 1.48)	1.20 (0.95, 1.51)	1.45 (1.09, 1.93)
Adjusting for alcohol and smoking (multiple imputation)	3260	14037	1.20 (1.06, 1.36)	1.17 (0.99, 1.39)	1.12 (0.82, 1.54)	1.17 (0.92, 1.48)	1.44 (1.08, 1.92)
Not adjusting for indications[c]	3260	14037	1.23 (1.09, 1.38)	1.19 (1.01, 1.40)	1.11 (0.81, 1.51)	1.23 (0.97, 1.55)	1.49 (1.13, 1.98)

Abbreviations: DDDs, Daily Defined Doses; OR, Odds Ratio.

[a]Except where otherwise stated model contains age, gastro-oesophageal reflux disease, Barrett's oesophagus, peptic ulcer, urinary tract infections/cystitis and charlson comorbidities (diabetes, myocardial infarction, coronary heart disease, heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic obstructive pulmonary disease, osteoporosis, severe mental illness, rheumatological disease, renal disease, liver disease, irritable bowel disease, human immunodeficiency viruses) and celecoxib use. [b]Adjusting for smoking categorised as non-smoker, ex-smoker, current smoker and current heavy smoker. [c]Model same as [a] but excluding gastro-oesophageal reflux disease, Barrett's oesophagus and peptic ulcer.