Ranitidine Use and Risk of Upper Gastrointestinal Cancers

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Research Article

Abstract

Ranitidine was removed from several markets following discovery that the drug was contaminated with *N*-nitrosodimethylamine, a suspected human carcinogen. However, evidence of increased cancer risk following ranitidine use remains inconclusive. According to our a priori hypothesis, ranitidine increases the risk of esophageal, stomach, liver and pancreatic cancer. We used the nationwide Danish Prescription Registry, to create a cohort of incident ranitidine users with two active comparator cohorts comprising users of other histamine-2 receptor blockers (H2RBs) and users of proton pump inhibitors (PPIs). Record linkage allowed virtually complete follow-up through 2018. All Danish residents aged 18 years or older with a first prescription of ranitidine, other H2RBs or PPIs in 1996 through 2008. Incidence of esophageal, stomach, liver or pancreatic cancer. We used Cox analyses, with propensity-score weighting to calculate hazard ratios (HRs) and 10-year cumulative risk with 95% confidence intervals (CIs). We ascertained 276 newly diagnosed esophageal, 342 stomach, 133 hepatocellular, and 517 pancreatic cancers among ranitidine users during follow-up (median 14 years). In comparison with use of other H2RBs or PPIs, we found no consistent evidence of increased HRs or excess 10-year cumulative risk of any upper gastrointestinal cancer following ranitidine use. We observed no association after restriction to subjects with at least 5 or 10 prescriptions or those with 10 prescriptions and at least 10 years of follow-up. Our large prospective study using high-quality prescription and cancer incidence data, with two active comparator groups, provided no compelling evidence that ranitidine increases the risk of upper gastrointestinal cancers.

Introduction

In 2019, contamination with *N*-nitrosodimethylamine (NDMA) was reported in the acid-reducing histamine-2 receptor blocker (H2RB) ranitidine, but not in other H2RBs (e.g., cimetidine and famotidine) [1]. NDMA, an *N*-nitroso compound, is classified by the International Agency for Research on Cancer as "probably carcinogenic to humans," based on "sufficient evidence" of carcinogenicity in animals and "no adequate data" in humans [2] Hence, ranitidine was recalled by several agencies.

However, at least two areas of profound uncertainty remain. First, the reported levels of NDMA contamination in ranitidine tablets differ by several orders of magnitude between laboratories [2], and the variation among batches and the impact of storage, transportation, temperature, and endogenous metabolism remain to be established. Second, while NDMA is an animal carcinogen, decades of research have not documented a causal association with any human cancer type or site [2], leaving unresolved questions about the impact of NDMA on human health, especially at concentrations reportedly detected in ranitidine.

Given these uncertainties, analyses of cancer risk following ranitidine use per se – rather than studies based on debatable estimates of NDMA exposure – are more informative about possibly increased cancer risk from use of this drug. Analyses focusing on upper gastrointestinal tract cancer, which is directly exposed to the drug, are also more likely to yield informative findings than analyses of other

cancer sites. Research on ranitidine use in relation to risk of cancers of the esophagus, stomach, pancreas, and liver has been inconclusive [3–9]. This lack of clarity stems in part from potential confounding by indication and reverse causality, which favor spurious positive association [3, 4, 7, 9]. In several studies of ranitidine and cancer risk, additional limitations include self-reported drug use, incomplete confounder adjustment, limited sample size, short follow-up, and conflation of disparate cancer types.

To reduce these concerns, we undertook a cohort study based on data from the Danish Prescription Registry. Its design emulated a randomized trial and thereby reduced confounding by indication [10] by comparing cancer risk between ranitidine users and an active comparator group comprising individuals prescribed other H2RBs. We included a second active comparator group of individuals prescribed proton pump inhibitors (PPIs), which are used for similar indications.

Methods

Data sources and study population

We conducted this study within the entire Danish population of approximately 5.8 million persons. All Danish residents are provided free access to health care [11]. Since 1968, the Civil Registration System has assigned a unique civil registration number to all residents at birth or upon immigration [12]. The System also records sex and date of birth, and tracks changes in vital status, and migration for the entire population. The registration number allows unambiguous record linkage at the individual level.

The Danish National Prescription Registry contains complete data on prescription medications dispensed from community pharmacies in Denmark since 1995 [13]. It does not include medications used in-hospital. We used this Registry (codes defined in supplementary material Table 1) to identify all adult (18 years or older) first-time users of ranitidine. We defined first-time users as persons who redeemed their first prescription for ranitidine between 1996 and 2008 and had no previous prescriptions for nizatidine, because nizatidine oral solution may contain high levels of NDMA [1]. As active comparators, we identified all adult first-time users of cimetidine or famotidine, hereafter categorized as other H2RBs, and PPIs, defined as persons who redeemed their first prescription for these drugs between 1996 and 2008 and had no previous prescriptions for ranitidine or nizatidine.

We defined the index date as the date of the first prescription. We allowed ranitidine users to redeem prescriptions for other H2RBs or PPIs, but censored users of other H2RBs and PPIs if they redeemed a ranitidine prescription during follow-up, with a 2-year lag-time. Statistics on over-the-counter use of H2RBs and PPIs have been available since 1999 in Denmark. The proportion of ranitidine defined daily doses (DDDs) sold by prescription was 84% in 1999, declining to approximately 50% in 2004–2011, and to approximately 20% in 2012–2017 (Supplementary Material Table 2). Similarly, the proportion of total H2RB DDDs sold by prescription was 83% in 1999, declining to 60% in 2004–2007, and with a further decline thereafter (data not available for 2010–2017). In contrast, 97–98% of PPIs were sold by prescription throughout the period.

We also retrieved information on use of selected drugs (defined in Supplementary Material Table 1) potentially associated with risk of upper gastrointestinal cancer and thiazolidinedione recorded before or on the index date with a 90-day look-back period. We also identified use of drugs associated with bleeding risk, including platelet inhibitors, and anticoagulants, as such drugs could alter the threshold for diagnosis of cancer.

The Danish National Patient Registry has recorded all inpatient admissions to all Danish hospitals since 1977, and hospital outpatient clinic and emergency room visits since 1995 [14]. We retrieved all diagnoses of gastrointestinal disease indicating H2RB treatment, including Barrett's esophagus, gastroesophageal reflux disease, and peptic ulcers, recorded before or on the index date, with a 10-year look-back period. We also retrieved data on other chronic diseases including diabetes, chronic obstructive pulmonary disease (COPD), ischemic heart disease, and alcohol-related disease (see Supplementary Material Table 3) for definitions and disease codes). The Danish Pathology Registry contains information coded using SNOMED on all specimens examined in Danish departments of pathology. From this Registry, we retrieved information on Barrett's esophagus diagnosed before or on the index date.

Follow-up

We followed members of the three cohorts starting one year after their index date (to avoid reverse causation) for an incident diagnosis of cancer recorded in the Danish Cancer Registry [15] which has recorded cancer diagnoses since 1943, with accurate and nearly complete case ascertainment. Cancer diagnoses are recorded using *International Classification of Diseases*, *Tenth Revision* (ICD-10) codes, and codes from the *ICD for Oncology, Third Revision* (ICD-O-3) for topography and morphology. The outcomes of interest were esophageal cancer (any, adenocarcinoma, and squamous cell carcinoma), stomach cancer (any, proximal, distal, and unknown/several regions), hepatocellular carcinoma, and pancreatic cancer. If a subject had cancer at more than one cancer site, all were included in the analysis. We excluded subjects with a cancer diagnosis recorded before the start of follow-up, except for non-melanoma skin cancer.

The Danish Register of Causes of Death includes age, place, and cause of death (coded according to ICD-10 since 1994) [16]. We obtained information on deaths due to cancer. We included cancer-specific deaths in the outcome definition if the cancer was not identified through the Cancer Registry.

The study was reported to the Danish Data Protection Agency through registration at Aarhus University, with exemption from informed consent (record number KEA2017-36/812).

Statistical analyses

Starting one year after the date of the first prescription, we followed cohort members until the diagnosis date of a cancer of interest for a given analysis (i.e., without censoring for other cancer types), date of death, emigration, or end of the period (31 December 2018), using an intention-to-treat approach. We censored users of other H2RBs and PPIs if they redeemed a ranitidine prescription, with a 2-year lag-time.

We computed the number of events (incident cancer or cancer-specific death) per person-years at risk and the 10-year cumulative risk (with death from other causes as a competing risk) of each cancer type by exposure status.

We used logistic regression, including all available covariates, to compute propensity scores for exposure to ranitidine. In the models, we included age and index dates as splines, along with use of PPIs in the previous two years when comparing with H2RBs and use of other H2RBs in the previous two years when comparing with PPIs. We then used the propensity scores to compute stabilized inverse-probability-of-treatment (sIPT) weights. We assessed the covariate balance after weighting using standardized mean differences. The use of sIPT weighting permitted estimation of the average treatment effect through comparison of exposed vs. unexposed populations with covariate distributions resembling the distribution in the overall population.

We compared the ranitidine-exposed cohort with each of the two comparison cohorts by estimating crude and sIPT-weighted risk curves, considering death from other causes as a competing risk. We obtained the 10-year cumulative risk and calculated crude and weighted 10-year risk differences with 95% confidence intervals (CIs) estimated by bootstrapping. We calculated hazard ratios (HRs) using Cox regression analysis including the crude and sIPT-weighted observations, with 95% CIs estimated by bootstrapping. We confirmed the proportionality assumption using log-log plots.

To address treatment duration, we conducted analyses restricted to persons who redeemed at least five or at least 10 prescriptions for ranitidine, other H2RBs, or PPIs. We started follow-up one year after the fifth prescription or the tenth prescription, respectively, and we included time between the first and the fifth/tenth prescription as a variable when computing propensity scores. In addition, in the analysis of subjects who redeemed at least 10 prescriptions, we separately analyzed the first 10 years of follow-up and follow-up after 10 + years, to focus on the subpopulation with relatively high exposure and long follow-up time.

We used SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) for analyses.

Results

Descriptive characteristics

Our study encompassed 103,565 first time users of ranitidine, 182,497 incident users of other H2RBs, and 807,725 incident users of PPIs. Table 1 summarizes characteristics of the three analytic cohorts. During median follow-up of 14 years (interquartile range (IQR), 10–18) among ranitidine users, we ascertained a total of 276 esophageal, 342 stomach, 133 hepatocellular, and 517 pancreatic cancers (Table 1).

Risk estimates

Figure 1 and Supplementary Material Fig. 1 shows sIPT weighted and crude HRs for each cancer site, respectively. In the primary analyses, which included individuals with at least one prescription of interest

during the entire follow-up period, all HRs except one were clustered around the null value of 1.0, whether ranitidine was compared with other H2RBs or with PPIs. In both comparisons, we found an approximately 30% increased risk of esophageal adenocarcinoma, but not esophageal squamous cell carcinoma, among ranitidine users. However, the 10-year cumulative risk difference between the ranitidine and the comparator cohorts was 0.02%–only marginally statistically significant (Fig. 1).

The pattern of results was virtually identical in analyses restricted to individuals with at least five prescriptions of ranitidine, other H2RBs, or PPIs (Supplementary Material Fig. 2), as well as after restriction to those with at least 10 prescriptions, although statistical precision was lower for the latter comparisons (Fig. 2). We found no evidence of an increase in risk with a larger number of prescriptions; on the contrary, HRs remained clustered around 1.0 in comparisons with other H2RBs and with PPIs, and no single HR was statistically significant. In the analysis of subjects with 10 or more prescriptions, the sIPT-weighted HR for adenocarcinoma of the esophagus was 0.97 (95% CI: 0.53 to 1.76) for ranitidine compared with other H2RBs, and 0.62 (95% CI 0.38 to 1.00) for ranitidine compared with PPIs.

We also analyzed the impact of follow-up time (i.e., latency) among subjects with 10 or more prescriptions. Due to small numbers, we analyzed each of the four cancer sites without further subgrouping of esophageal and stomach cancers. Case numbers were insufficient (n < 10 among ranitidine users) to estimate the risk of liver cancer after more than 10 years of follow-up. We found no evidence of higher risk for esophageal, stomach, or pancreatic cancer in association with long-term use of ranitidine vs. other H2RBs or PPIs (Fig. 3).

Discussion

In this large, population-based study using high-quality exposure and outcome data, we consistently observed HRs and risk differences close to unity when use of ranitidine was compared with use of either other H2RBs or PPIs. Analyses by number of prescriptions and duration of follow-up showed no evidence of trends. Although analyses restricted to participants with at least five or 10 prescriptions relied on smaller numbers of incident cancers, the estimates remained clustered around one, with no evidence of significantly increased risk of any evaluated malignancy.

Because we calculated many estimates, some (on average 1 in 20) are expected to be significant due to chance. Thus, chance might explain the modest excess risk of esophageal adenocarcinoma among ranitidine users compared with users of other H2RBs or PPIs. The observed associations are unlikely to be due to confounding by indication, which was similar among comparison groups, or by lifestyle factors such as smoking and alcohol use, which are causes of esophageal squamous cell carcinoma but not adenocarcinoma. If a causal association existed, we would expect to observe stronger associations with a larger number of prescriptions and, most likely, with longer follow-up, yet such patterns were not evident.

Strengths of our study include its population-based design, with two active comparator groups that emulate a randomized trial; unbiased assessment of prescriptions; the ability to identify first time rather

than prevalent users of the drugs by application of a 1-year lag time; the separate assessment of etiologically distinct cancer types identified through linkage to the Cancer Registry; the use of propensity scores to adjust for confounding at baseline; and complete follow-up for cancer. Although approximately half of ranitidine users had only one prescription, a substantial number had five or even ten prescriptions, enabling analyses of long-term exposure with up to 20 years of follow-up.

Our study also has limitations. Because malignant transformation of cancer may take longer than 20 years, the most severe shortcoming of our study is the limited number of participants with long-term follow-up. Second, the Prescription Registry provides no information about drugs removed from the Danish market, nor about compliance with prescriptions or use of drugs sold over-the-counter. Because the drugs examined relieve severe gastrointestinal symptoms, compliance with prescriptions was probably high, at least for chronic use. Although we were able to rely on the Prescription Registry to identify most ranitidine users with the longest follow-up (i.e., those first prescribed ranitidine in 1999–2001; Supplementary Material Table 3), over-the-counter use inevitably led to underestimation of ranitidine exposure, as well as exposure to other H2RBs, in more recent years. The potential direction of bias in HR estimates is unclear, but the magnitude of any bias would be limited in the comparison between users of ranitidine and other H2RBs, since all major H2RBs were similarly impacted by over-the-counter use over time.

Comparison of our results with those in the literature on ranitidine and risk of upper gastrointestinal cancers is hampered by differences in study design. The few earlier studies were limited by evidence of reverse causality, confounding by indication, small sample size, shorter follow-up time, or combination of malignancies with different etiologies [3–9]. Two studies detected a higher risk of upper gastrointestinal cancers following use of PPIs compared to H2RBs [7, 9] whilst one study found a similar risk of liver cancer among users and non-users of ranitidine and among users and non-users of other H2RBs [7].

Only two cohort studies attempted to emulate a randomized trial by including an active comparator cohort and restricting the analyses to incident users of PPIs or H2RBs. In the first study, which followed US veterans for cause-specific mortality over a median duration of 10 years [9], a 41% higher mortality from all upper gastrointestinal cancers combined was observed among PPI users compared with H2RB users (90% of whom used ranitidine). Hence, this study provided no information on whether ranitidine itself or NDMA contamination increased the risk of any cancer by type or at any particular site. However, its findings suggest that if a causal effect exists, the risk is further increased following use of PPIs. The second study used a claims database in Japan [5] to follow users of ranitidine/nizatidine or other H2RBs for cancer incidence over a median duration of 2.4 years. Despite its careful design, it found no significant differences in the risk of overall or any site-specific cancers, including stomach, pancreatic, and other sites (but not esophagus or liver, which were not analyzed separately). However, the short duration of follow-up limited inferences based on these findings.

We conclude that our study provides little evidence that ranitidine, whether through NDMA contamination or any other reason, increases risk of upper gastrointestinal cancers. This conclusion pertains to the

prevailing duration of treatment in Denmark and presumably also in other countries. Studies of individuals with longer exposure may not be feasible because ranitidine now has been removed from several markets worldwide. Hence, extended follow-up of our cohort may be the most realistic and informative approach to understanding the human health impact, if any, of NDMA contamination of ranitidine.

Declarations

Availability of data and material

Because our study was based entirely on nationwide registers in Denmark, we have no mandate to share data.

Code availability

Not applicable.

Ethics approval

The study was reported to the Danish Data Protection Agency through registration at Aarhus University, with exemption from informed consent (record number KEA2017-36/812).

Consent to participate

Because this study was based entirely on record linkage data collected from 1995 and onwards, patient/public involvement was not feasible.

Consent for publication

Not required.

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Table

Table 1

Baseline Characteristics of Cohort Participants by Type of Acid Suppressive Drug: Ranitidine, Other H2-Receptor Blockers (H2RBs), and Proton Pump Inhibitors (PPIs).

	H2RBs		PPIs
Characteristics	Ranitidine, N (%)	Other, N (%)	N (%)
Total number	103,565	182,497	807,725
Men	44,222 (42.7)	76,829 (42.1)	364,134 (45.1)
Women	59,343 (57.3)	105,668 (57.9)	443,591 (54.9)
Age at first prescription, median (IQR), years	50 (36–64)	45 (32–60)	52 (37–66)
Marital status			
Married	55,934 (54.0)	94,289 (51.7)	433,008 (53.6)
Divorced	12,458 (12.0)	20,454 (11.2)	94,540 (11.7)
Widowed	10,292 (9.9)	15,472 (8.5)	91,346 (11.3)
Single	24,881 (24.0)	52,282 (28.6)	188,831 (23.4)
Time period of first prescription			
1996–1999	39,717 (38.3)	96,386 (52.8)	197,011 (24.4)
2000–2003	27,658 (26.7)	56,706 (31.1)	231,615 (28.7)
2004–2008	36,190 (34.9)	29,405 (16.1)	379,099 (46.9)
Underlying gastrointestinal disease			
Gastroesophageal reflux disease	2,680 (2.6)	2,275 (1.2)	20,417 (2.5)
Barrett's esophagus	262 (0.3)	192 (0.1)	1,656 (0.2)
Gastric or duodenal ulcer	3,038 (2.9)	3,348 (1.8)	38,203 (4.7)
Other comorbidities at baseline			
Alcohol-related disease	4,630 (4.5)	7,577 (4.2)	38,897 (4.8)
Myocardial infarction	2,091 (2.0)	2,552 (1.4)	22,235 (2.8)
Chronic obstructive lung disease	4,772 (4.6)	6,753 (3.7)	41,832 (5.2)
Connective tissue disease	2,131 (2.1)	2,962 (1.6)	19,968 (2.5)
Moderate to severe renal disease	691 (0.7)	971 (0.5)	9,806 (1.2)
Congestive heart disease	1,531 (1.5)	1,770 (1.0)	19,517 (2.4)

	H2RBs		PPIs
Cerebrovascular disease	1,925 (1.9)	2,384 (1.3)	18,742 (2.3)
Dementia	3,190 (3.1)	4,028 (2.2)	35,401 (4.4)
Mild liver disease	772 (0.7)	970 (0.5)	8,485 (1.1)
Moderate to severe liver disease	139 (0.1)	159 (0.1)	2,414 (0.3)
Diabetes type 1	1,023 (1.0)	1,228 (0.7)	9,941 (1.2)
Diabetes type 2	2,119 (2.0)	2,453 (1.3)	20,586 (2.5)
Diabetes with end-organ damage	1,305 (1.3)	1,473 (0.8)	14,223 (1.8)
Hemiplegia	152 (0.1)	178 (0.1)	1,449 (0.2)
AIDS	61 (0.1)	111 (0.1)	742 (0.1)
Medications used before/at baseline			
NSAIDs	17,559 (17.0)	29,323 (16.1)	147,594 (18.3)
Low-dose aspirin and other platelet inhibitors	8,329 (8.0)	10,003 (5.5)	87,943 (10.9)
Oral anticoagulants	1,049 (1.0)	785 (0.4)	13,322 (1.6)
Thiazolidinedione	41 (0.0)	15 (0.0)	379 (0.0)
Number of incident cancers during follow-up			
Esophageal, any	276 (0.3)	392 (0.2)	2,072 (0.3)
Adenocarcinoma	115 (0.1)	133 (0.1)	715 (0.1)
Squamous cell carcinoma	73 (0.1)	114 (0.1)	671 (0.1)
Stomach, any	342 (0.3)	560 (0.3)	2,523 (0.3)
Proximal	154 (0.1)	251 (0.1)	1,144 (0.1)
Distal	71 (0.1)	151 (0.1)	567 (0.1)
Unknown/several regions	196 (0.2)	287 (0.2)	1,289 (0.2)
Hepatocellular carcinoma	133 (0.1)	228 (0.1)	1,322 (0.2)
Pancreatic cancer	517 (0.5)	835 (0.5)	3,855 (0.5)
Follow-up, years [median (IQR)]	14 (10−18)	16 (11−19)	12 (9−16)

Figures

Ranitidine versus Other H2RBs	Ranitidine Events/Person years	Comparison Events/Person years	Hazard ratio (95%CI)	Ranitidine 10 year Risk, %	Comparison 10 year Risk, %	10 year Risk difference (95%CI), %
Esophageal cancer	261 / 1,522,653	398 / 2,534,090	1.09 (0.91–1.29)	0.14 (0.12 - 0.17)	0.13 (0.11 - 0.15)	0.02 (-0.01–0.04)
adenocarcinoma	105 / 1,522,808	133 / 2,534,288	1.30 (1.01–1.68)	0.06 (0.04 - 0.07)	0.04 (0.03 - 0.05)	0.02 (0.00–0.03)
squamous cell carcinoma	73 / 1,522,905	113 / 2,534,393	1.07 (0.80–1.44)	0.04 (0.03 - 0.06)	0.04 (0.03 - 0.05)	0.00 (-0.01–0.02)
Stomach cancer	331 / 1,522,485	564 / 2,533,517	0.98 (0.84–1.14)	0.19 (0.16 - 0.22)	0.20 (0.18 - 0.22)	-0.01 (-0.04–0.02)
proximal	149 / 1,522,796	257 / 2,534,075	0.96 (0.76–1.21)	0.07 (0.06 - 0.09)	0.09 (0.07 - 0.10)	-0.01 (-0.04–0.01)
distal	65 / 1,522,863	151 / 2,534,155	0.72 (0.54–0.97)	0.05 (0.03 - 0.06)	0.06 (0.05 - 0.07)	-0.01 (-0.03–0.01)
unknown/several regions	191 / 1,522,846	283 / 2,534,330	1.13 (0.93–1.36)	0.11 (0.10 - 0.14)	0.10 (0.09 - 0.12)	0.01 (-0.01–0.04)
Hepatocellular carcinoma	127 / 1,522,856	235 / 2,534,285	0.89 (0.72–1.10)	0.06 (0.05 - 0.08)	0.07 (0.05 - 0.08)	0.00 (-0.02–0.02)
Pancreatic cancer	498 / 1,522,599	850 / 2,533,886	0.97 (0.87–1.10)	0.28 (0.25 - 0.32)	0.27 (0.25 - 0.30)	0.01 (-0.03–0.06)

0.25   3 | -0.25   0.25

Ranitidine versus PPIs	Ranitidine Events/Person years	Comparison Events/Person years	Hazard ratio (95%CI)	Ranitidine 10 year Risk, %	Comparison 10 year Risk, %	10 year Risk difference (95%CI), %
Esophageal cancer	283 / 1,290,801	2,074 / 9,629,278	1.01 (0.90–1.14)	0.19 (0.17 - 0.22)	0.17 (0.16 - 0.18)	0.02 (-0.01–0.05)
adenocarcinoma	123 / 1,290,945	716 / 9,630,580	1.27 (1.04–1.56)	0.08 (0.06 - 0.11)	0.06 (0.05 - 0.06)	0.03 (0.00–0.05)
squamous cell carcinoma	68 / 1,291,076	669 / 9,630,798	0.76 (0.60–0.96)	0.05 (0.04 - 0.06)	0.06 (0.06 - 0.07)	-0.01 (-0.03–0.00)
Stomach cancer	349 / 1,290,655	2,533 / 9,627,031	1.03 (0.92–1.16)	0.24 (0.21 - 0.28)	0.23 (0.22 - 0.24)	0.01 (-0.02–0.04)
proximal	158 / 1,290,974	1,146 / 9,629,693	1.02 (0.86–1.22)	0.10 (0.08 - 0.13)	0.10 (0.09 - 0.10)	0.00 (-0.02–0.03)
distal	74 / 1,291,000	570 / 9,630,314	0.98 (0.77–1.24)	0.06 (0.05 - 0.08)	0.05 (0.05 - 0.06)	0.00 (-0.01–0.02)
unknown/several regions	196 / 1,291,024	1,297 / 9,630,522	1.13 (0.96–1.33)	0.14 (0.11 - 0.16)	0.12 (0.12 - 0.13)	0.01 (-0.01–0.04)
Hepatocellular carcinoma	153 / 1,291,005	1,311 / 9,630,519	0.86 (0.71–1.05)	0.10 (0.08 - 0.12)	0.11 (0.10 - 0.12)	-0.01 (-0.04–0.01)
Pancreatic cancer	511 / 1,290,806	3,861 / 9,628,916	0.99 (0.89–1.09)	0.35 (0.31 - 0.40)	0.34 (0.33 - 0.35)	0.01 (-0.03–0.06)

0.25   3 | -0.25   0.25

Figure 1

Stabilized Inverse-Probability-of-Treatment-Weighted Comparison of Risk of Cancer in Users of ranitidine Versus Users of Other H2RBs/PPIs. Logistic regression was used to estimate the propensity of ranitidine exposure. This model included age (as a spline), index date (as a spline), previous use of PPIs, previous use of other H2RBs, as well as sex, marital status, underlying gastrointestinal diseases, comorbidities, use of NSAIDs, thiazolidinedione, low-dose aspirin, and oral anticoagulants, respectively. Propensity scores for ranitidine exposure were used to compute the stabilized inverse probability of treatment weights. Hazard ratios were estimated using Cox proportional hazard regression analysis. Stabilized inverse-probability-of-treatment-weighted number of cancers per person-years of follow-up, hazard ratio for cancer, 10-year cumulative cancer incidence (risk) with death as a competing risk, and 10-year risk differences comparing ranitidine initiators with initiators of other H2-receptor blockers (top) and comparing ranitidine initiators with initiators of proton pump inhibitors (PPIs). Follow-up started 1 year after the first prescription.

Ranitidine versus Other H2RBs

Ranitidine versus Other H2RBs	Ranitidine Events/Person years	Comparison Events/Person years	Hazard ratio (95%CI)	Ranitidine 10 year Risk, %	Comparison 10 year Risk, %	10 year Risk difference (95%CI), %
Esophageal cancer	65 / 159,816	45 / 130,515	1.16 (0.80–1.69)	0.28 (0.21 - 0.38)	0.26 (0.19 - 0.37)	0.02 (-0.10–0.14)
adenocarcinoma	22 / 159,856	19 / 130,537	0.97 (0.53–1.76)	0.11 (0.06 - 0.18)	0.11 (0.06 - 0.18)	0.00 (-0.08–0.08)
squamous cell carcinoma	17 / 159,863	8 / 130,556	N/A	N/A	N/A	N/A
Stomach cancer	75 / 159,814	54 / 130,475	1.13 (0.77–1.65)	0.31 (0.23 - 0.42)	0.34 (0.23 - 0.48)	-0.03 (-0.18–0.13)
proximal	48 / 159,829	31 / 130,507	1.25 (0.73–2.13)	0.20 (0.13 - 0.30)	0.18 (0.10 - 0.32)	0.02 (-0.12–0.15)
distal	5 / 159,886	12 / 130,547	N/A	N/A	N/A	N/A
unknown/several regions	38 / 159,886	21 / 130,548	1.44 (0.88–2.38)	0.17 (0.11 - 0.26)	0.15 (0.09 - 0.22)	0.02 (-0.07–0.11)
Hepatocellular carcinoma	23 / 159,871	24 / 130,529	0.79 (0.43–1.44)	0.12 (0.07 - 0.20)	0.15 (0.09 - 0.25)	-0.03 (-0.12–0.06)
Pancreatic cancer	83 / 159,811	83 / 130,527	0.81 (0.60–1.09)	0.45 (0.34 - 0.60)	0.44 (0.33 - 0.58)	0.01 (-0.15–0.18)

Ranitidine versus PPIs

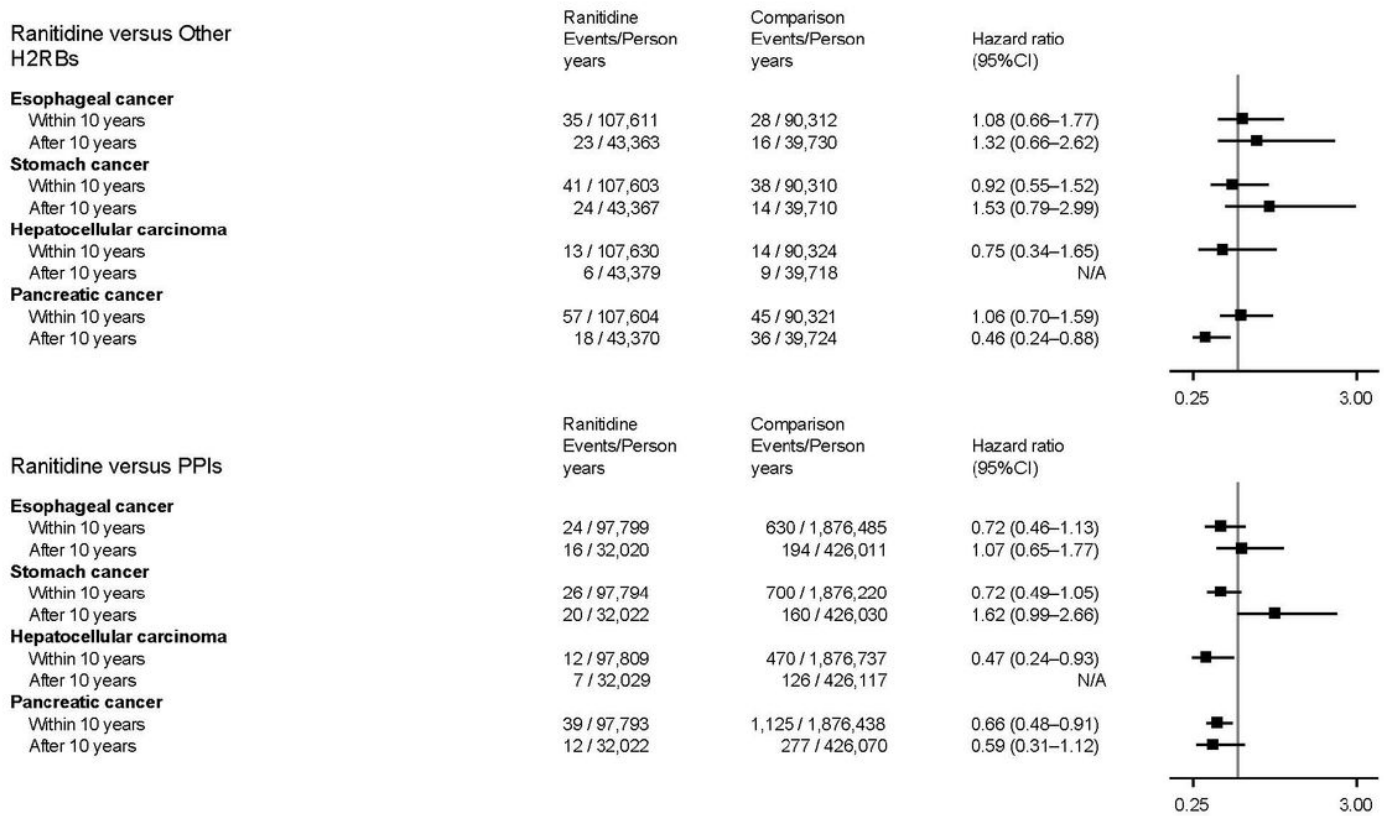| Ranitidine versus PPIs	Ranitidine Events/Person years	Comparison Events/Person years	Hazard ratio (95%CI)	Ranitidine 10 year Risk, %	Comparison 10 year Risk, %	10 year Risk difference (95%CI), %
Esophageal cancer	39 / 125,594	859 / 2,343,948	0.84 (0.61–1.15)	0.21 (0.14 - 0.31)	0.29 (0.27 - 0.31)	-0.08 (-0.17–0.01)
adenocarcinoma	12 / 125,608	355 / 2,344,316	0.62 (0.38–1.00)	0.07 (0.04 - 0.11)	0.12 (0.11 - 0.13)	-0.05 (-0.09– -0.02)
squamous cell carcinoma	12 / 125,622	217 / 2,344,680	1.06 (0.49–2.28)	0.05 (0.01 - 0.24)	0.07 (0.06 - 0.09)	-0.02 (-0.08–0.04)
Stomach cancer	44 / 125,588	887 / 2,343,541	0.92 (0.68–1.23)	0.23 (0.15 - 0.33)	0.31 (0.28 - 0.33)	-0.08 (-0.17–0.01)
proximal	26 / 125,598	454 / 2,344,150	1.05 (0.73–1.51)	0.14 (0.09 - 0.22)	0.16 (0.14 - 0.18)	-0.02 (-0.09–0.05)
distal	3 / 125,625	176 / 2,344,564	N/A	N/A	N/A	N/A
unknown/several regions	22 / 125,625	423 / 2,344,642	0.97 (0.63–1.50)	0.12 (0.07 - 0.20)	0.14 (0.13 - 0.16)	-0.02 (-0.09–0.04)
Hepatocellular carcinoma	20 / 125,616	602 / 2,344,420	0.61 (0.35–1.08)	0.13 (0.07 - 0.28)	0.20 (0.19 - 0.22)	-0.07 (-0.16–0.03)
Pancreatic cancer	51 / 125,582	1,447 / 2,344,003	0.66 (0.50–0.86)	0.35 (0.26 - 0.47)	0.50 (0.47 - 0.53)	-0.15 (-0.26– -0.04)

Figure 2

Stabilized Inverse-Probability-of-Treatment-Weighted Comparison of Risk of Cancer in Users of Ranitidine Versus Users of Other H2RBs/PPIs Restricted to Patients with at least 10 Filled Prescriptions. Logistic regression was used to estimate the propensity of ranitidine exposure. This model included age (as a spline), index date (as a spline), previous use of PPIs, previous use of other H2RBs, time between 1st and 10th prescription (as a spline), as well as sex, marital status, underlying gastrointestinal diseases, comorbidities, and use of NSAIDs, thiazolidinedione, low-dose aspirin, and oral anticoagulants, respectively. Propensity scores for ranitidine exposure were used to compute the stabilized inverse probability of treatment weights. Hazard ratios were estimated using Cox proportional hazard regression analysis. Stabilized inverse-probability-of-treatment-weighted number of cancers per person-years of follow-up, hazard ratio for cancer, 10-year cumulative cancer incidence (risk) with death from other causes as a competing risk, and 10-year risk differences comparing ranitidine initiators with initiators of other H2-receptor blockers (top) and comparing ranitidine initiators with initiators of proton pump

inhibitors (PPIs). The analysis was restricted to subjects with at least 10 prescriptions for the specific drug, with follow-up starting one year after the date of the 10th prescription.

Ranitidine versus Other H2RBs	Ranitidine Events/Person years	Comparison Events/Person years	Hazard ratio (95%CI)	
Esophageal cancer				
Within 10 years	35 / 107,611	28 / 90,312	1.08 (0.66–1.77)	
After 10 years	23 / 43,363	16 / 39,730	1.32 (0.66–2.62)	
Stomach cancer				
Within 10 years	41 / 107,603	38 / 90,310	0.92 (0.55–1.52)	
After 10 years	24 / 43,367	14 / 39,710	1.53 (0.79–2.99)	
Hepatocellular carcinoma				
Within 10 years	13 / 107,630	14 / 90,324	0.75 (0.34–1.65)	
After 10 years	6 / 43,379	9 / 39,718	N/A	
Pancreatic cancer				
Within 10 years	57 / 107,604	45 / 90,321	1.06 (0.70–1.59)	
After 10 years	18 / 43,370	36 / 39,724	0.46 (0.24–0.88)	

Ranitidine versus PPIs	Ranitidine Events/Person years	Comparison Events/Person years	Hazard ratio (95%CI)	
Esophageal cancer				
Within 10 years	24 / 97,799	630 / 1,876,485	0.72 (0.46–1.13)	
After 10 years	16 / 32,020	194 / 426,011	1.07 (0.65–1.77)	
Stomach cancer				
Within 10 years	26 / 97,794	700 / 1,876,220	0.72 (0.49–1.05)	
After 10 years	20 / 32,022	160 / 426,030	1.62 (0.99–2.66)	
Hepatocellular carcinoma				
Within 10 years	12 / 97,809	470 / 1,876,737	0.47 (0.24–0.93)	
After 10 years	7 / 32,029	126 / 426,117	N/A	
Pancreatic cancer				
Within 10 years	39 / 97,793	1,125 / 1,876,438	0.66 (0.48–0.91)	
After 10 years	12 / 32,022	277 / 426,070	0.59 (0.31–1.12)	

Figure 3

Stabilized Inverse-Probability-of-Treatment-Weighted Hazard Ratio of Cancer in Users of Ranitidine Versus Users of Other H2RBs/PPIs Restricted to Patients with at least 10 Filled Prescriptions within 10 Years of Follow-Up and after 10 Years of Follow-Up. Logistic regression was used to estimate the propensity of ranitidine exposure. This model included age (as a spline), index date (as a spline), previous use of PPIs, previous use of other H2RBs, time between 1st and 10th prescription (as a spline) as well as sex, marital status, underlying gastrointestinal diseases, comorbidities, use of NSAIDs, thiazolidinedione, low-dose aspirin, and oral anticoagulants, respectively. Propensity scores for ranitidine exposure were used to compute the stabilized inverse probability of treatment weights. Hazard ratios were estimated using Cox proportional hazard regression analysis. Stabilized inverse-probability-of-treatment weighted number of cancers per person-year of follow-up, hazard ratio for cancer comparing ranitidine initiators with initiators of other H2-receptor blockers (top) and comparing ranitidine initiators with initiators of proton pump inhibitors (PPIs). The analysis was restricted to subjects with at least 10 prescriptions for the specific drug, and follow-up was categorized as 1 to <10 years or 10 or more years.

Supplementary Files

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- Supplementarymaterial.docx