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ORIGINAL ARTICLE

# Ranitidine Use and Gastric Cancer Among Persons with *Helicobacter pylori*

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## Abstract

**Background** The Food and Drug Administration requested withdrawal of ranitidine formulations, due to a potentially carcinogenic contaminant, N-nitrosodimethylamine.

**Aims** We evaluate whether ranitidine use is associated with gastric cancer.

**Methods** This is a retrospective multicenter, nationwide cohort study within the Veterans Health Administration, among patients with *Helicobacter pylori* (HP) prescribed long-term acid suppression with either: (1) ranitidine, (2) other histamine type 2 receptor blocker (H2RB), or (3) proton pump inhibitor (PPI)) between May 1, 1998, and December 31, 2018. Covariates included race, ethnicity, smoking, age, HP treatment, HP eradication. Primary outcome was non-proximal gastric adenocarcinomas, using multivariable Cox proportional hazards analysis.

**Results** We identified 279,505 patients with HP prescribed long-term acid suppression (median 53.4 years; 92.9% male). Compared to ranitidine, non-ranitidine H2RB users were more likely to develop cancer (HR 1.83, 95%CI 1.36–2.48); PPI users had no significant difference in future cancer risk (HR 0.92, 95% CI 0.82–1.04), $p < 0.001$. Demographics associated with future cancer included increasing age (HR 1.18, 95% CI 1.15–1.20, $p < 0.001$), Hispanic/Latino ethnicity (HR 1.46, 95% CI 1.21–1.75, $p < 0.001$), Black race (HR 1.89, 95% CI 1.68–2.14) or Asian race (HR 2.03, 95% CI 1.17–3.52), $p < 0.001$, and gender (female gender HR 0.64, 95% CI 0.48–0.85, $p = 0.02$). Smoking was associated with future cancer (HR 1.38, 95% CI 1.23–1.54, $p < 0.001$). Secondary analysis demonstrated decreased cancer risk in those with confirmed HP eradication (HR 0.24, 95% CI 0.14–0.40). No association between ranitidine and increased gastric cancer was found.

**Conclusion** There is no demonstrable association between ranitidine use and future gastric cancer among individuals with HP on long-term acid suppression.

**Keywords** Gastric cancer · Pharmacoepidemiology · Acid suppression · Cancer risk

## Abbreviations

| | |
|---|---|
| CDW | Corporate Data Warehouse |
| FDA | Food and Drug Administration |
| H2RB | Histamine type 2 receptor blockers |
| HP | *Helicobacter pylori* |
| GC | Gastric cancer |
| ICD | International Classification of Diseases |
| NDMA | N-nitrosodimethylamine |
| OTC | Over-the-counter |
| PPI | Proton pump inhibitor |
| VHA | Veterans Health Administration |

## Introduction

As a selective histamine type 2 receptor blocker (H2RB), ranitidine has been widely used to treat and prevent acid-related gastrointestinal disorders, and at one point, was the best-selling drug in history [1]. On April 1, 2020, the US Food and Drug Administration (FDA) requested manufacturers withdraw all prescription and over-the-counter (OTC) ranitidine formulations from the market [2]. This was the culmination of an ongoing investigation, due to concern

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of a potentially carcinogenic contaminant, N-nitrosodimethylamine (NDMA), in ranitidine medications that are imperfectly stored [2, 3]. NDMA is potently carcinogenic in animal models and has been associated with gastric and colorectal cancers in population-based studies of humans [4–8]. Therefore, there is concern that NDMA from ranitidine could result in increased risk of gastric cancer in exposed patients.

The association between potentially NDMA-contaminated ranitidine and gastric cancers (GCs) is particularly difficult to elucidate given that (1) patients take ranitidine and other H2RBs for symptomatic control of what may be another underlying disease that can itself predispose to GC, (2) there have been as of yet unresolved questions about the use of long-term acid suppressants, both H2RBs and proton pump inhibitors (PPIs), and future GC risk [9–11], and (3) unlike many other cancers, GC has a well-known risk factor, *Helicobacter pylori* (HP), that must be considered. HP is considered a causative agent in the carcinogenic pathway for non-cardia gastric adenocarcinomas, and the World Health Organization has labeled it a class 1 carcinogen [12–14]. Thus, detangling any association between NDMA-contaminated ranitidine and GC requires consideration of HP status, patient population, and potential adverse/salutary effects of acid suppression medications as a whole. We utilized data from the largest US cohort of patients with HP to evaluate the interrelationship of HP, ranitidine, and GC [15].

## Methods

This retrospective cohort study was conducted within the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW), which includes data from the electronic medical record of all VHA facilities from 1994 onwards.

### Study Cohort

We utilized a cohort of patients with HP infection, which has been extensively described elsewhere, with details provided in the Supplement [15–18]. Briefly, patients with HP infection were included based on: (1) endoscopic pathology, (2) positive stool antigen test, (3) positive urea breath test, (4) prescription for one of 11 accepted eradication regimens for HP therapy as recommended by the American College of Gastroenterology, or (5) HP-associated International Classification of Diseases (ICD) 9/10 codes [19–22]. For patients with multiple criteria, the criterion with the earliest date was used. For those who had a prescription or administrative code as initial HP diagnosis without a diagnostic test that confirmed infection, we queried to identify whether serum antibody was tested within 90 days of HP diagnosis.

We included patients those who had been prescribed an acid-suppressing medication for at least 30 days. These were categorized as: (1) ranitidine, (2) non-ranitidine H2RBs: (cimetidine, nizatidine, famotidine), (3) or PPI: (esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole).

### Study Outcome

The outcome of interest for all analyses was nonproximal gastric adenocarcinoma (referred to as GC), identified using Veterans Affairs Clinical Cancer Registry and/or ICD 9/10 codes (Supplement) [23]. The diagnosis of GC was minimum 30 days after HP diagnosis to ensure testing was for HP, not a malignancy workup. We filtered to avoid capturing non-adenocarcinomas and cardia/gastroesophageal junction tumors, as these are less clearly associated with HP and nitrosamine intake [24–27].

Patients were followed until (1) cancer diagnosis, (2) death, (3) switching to a different acid suppressant category, or (4) December 1, 2018 (whichever was earliest).

### Statistical Analysis

We identified the earliest medication class that patients were taking within 15 years of last follow-up. We excluded those who had acid suppression initiated within 3 months of end of follow-up or less than 3 months total follow-up time. Utilizing a multivariable cox proportional hazards model, we evaluated the association of GC and acid suppressant category. We evaluated the following covariates shown to be associated with GC: age, gender, race, ethnicity, history of ever smoking (current or prior diagnostic code) [28], and zip code-level poverty at HP diagnosis. Zip code-level poverty was based on 2010 census data, categorized based on percentage of people within a zip code below the federal poverty line.

A secondary analysis sought to evaluate the impact of HP treatment and eradication status on future GCs. This analysis was restricted to those who had a positive diagnostic test for HP. Eradication status was defined as persistent infection, confirmed HP eradication, unknown eradication status (Supplement). We excluded patients who had eradication testing via endoscopy within 90 days of eventual cancer diagnosis, as this was possibly performed for alarm symptoms, versus eradication testing alone. This analysis also included as a covariate whether the patient received treatment of HP, considered to be treatment prescribed within the VHA after HP diagnosis, as defined above.

Stata/IC 15.1 (College Station, TX) was used to perform backward selection, with inclusion of all clinically significant hazard ratios (ORs), $p < 0.10$ for the purpose of model

building. All statistical tests were two-tailed, with results achieving significance at predefined level of $p < 0.05$. The Institutional Review Board of the Corporal Michael J. Crescenz VA Medical Center approved this study.

## Results

We identified 279,505 patients with detected HP who had been prescribed at least 30 days of an acid suppressant medication (median age 53.4; 92.9% male). Median follow-up was 4.4 years, IQR 1.7–9.2 years. Of the 279,505 patients, 69,157 (24.7%) were prescribed ranitidine, 6,559 (2.4%) another H2RB, and 203,789 (72.9%) a PPI (Table 1). Of those who were prescribed ranitidine, 20.7% were of Black or African American race, as compared to 13.1% in the non-ranitidine H2RB group and 25.9% in the PPI group ($p < 0.001$). Of those who were prescribed ranitidine, 76.4% were not of Hispanic or Latino ethnicity, as compared to 66.6% in the non-ranitidine H2RB group and 81.8% in the PPI group ($p < 0.001$). Development of GC was similar among all groups (Fig. 1).

Table 2 displays results of a multivariable Cox proportional hazard model evaluating the relationship between the

**Table 1** Comparison of patients with *H pylori* by acid suppressant medication

| | Ranitidine ($n = 69,157$) | Non-ranitidine H2RB ($n = 6559$) | PPI ($n = 203,789$) | $p$ value |
|---|---|---|---|---|
| Age at HP diagnosis, median (IQR) | 64.1 (55.0, 73.3) | 69.6 (60.4, 77.0) | 61.4 (52.6, 69.9) | < 0.001 |
| Male (%) | 65,167 (94.2%) | 6371 (97.1%) | 188,225 (92.4%) | < 0.001 |
| Race | | | | < 0.001 |
| White | 41,297 (59.7%) | 3724 (56.8%) | 120,961 (59.4%) | |
| Black or African American | 14,296 (20.7%) | 858 (13.1%) | 52,850 (25.9%) | |
| American Indian or Alaskan Native | 568 (0.8%) | 44 (0.7%) | 1864 (0.9%) | |
| Asian | 301 (0.4%) | 23 (0.4%) | 1390 (0.7%) | |
| Native Hawaiian or other Pacific Islander | 607 (0.9%) | 49 (0.7%) | 2212 (1.1%) | |
| Unknown | 12,088 (17.5%) | 1861 (28.4%) | 24,512 (12.0%) | |
| Ethnicity | | | | < 0.001 |
| Not Hispanic / Latino | 52,807 (76.4%) | 4370 (66.6%) | 166,671 (81.8%) | |
| Hispanic or Latino | 6565 (9.5%) | 436 (6.6%) | 19,109 (9.4%) | |
| Unknown | 9785 (14.1%) | 1753 (26.7%) | 18,009 (8.8%) | |
| Ever smoker (%) | 19,339 (28.0%) | 1538 (23.4%) | 58,957 (28.9%) | < 0.001 |
| Poverty level of zip code where patient resided at HP diagnosis | | | | < 0.001 |
| < 10% residing below poverty level | 10,645 (15.4%) | 1089 (16.6%) | 39,462 (19.4%) | |
| 10–24.9% residing below poverty level | 34,401 (49.7%) | 3219 (49.1%) | 102,161 (50.1%) | |
| 25–49.9% residing below poverty level | 18,609 (26.9%) | 1796 (27.4%) | 48,047 (23.6%) | |
| ≥ 50% residing below poverty level | 2481 (3.6%) | 168 (2.6%) | 5314 (2.6%) | |
| Unknown | 3021 (4.4%) | 287 (4.4%) | 8805 (4.3%) | |
| Method of HP diagnosis | | | | < 0.001 |
| Pathology | 3704 (5.4%) | 201 (3.1%) | 17,300 (8.5%) | |
| Stool Antigen | 1487 (2.2%) | 99 (1.5%) | 4985 (2.4%) | |
| Urea Breath Test | 52 (0.1%) | 5 (0.1%) | 166 (0.1%) | |
| RX, no serum Ab | 51,353 (74.3%) | 5220 (79.6%) | 138,755 (68.1%) | |
| ICD, no serum Ab | 1232 (1.8%) | 50 (0.8%) | 6140 (3.0%) | |
| RX, with serum Ab | 1546 (2.2%) | 181 (2.8%) | 4163 (2.0%) | |
| ICD, with serum Ab | 9783 (14.1%) | 803 (12.2%) | 32,280 (15.8%) | |
| Category of second medication, if patient switched after first | | | | < 0.001 |
| Ranitidine | – | 2607 (47.8%) | 31,592 (92.9%) | |
| Non-ranitidine H2RB | 1316 (2.6%) | – | 2428 (7.1%) | |
| PPI | 48,908 (97.4%) | 2842 (52.2%) | – | |
| Develop nonproximal gastric adenocarcinoma | 367 (0.5%) | 49 (0.7%) | 1108 (0.5%) | 0.07 |

*HP H pylori*, *H2RB* histamine type 2 receptor blockers, *ICD* International Classification of Diseases, *PPI* proton pump inhibitor, *RX* prescription

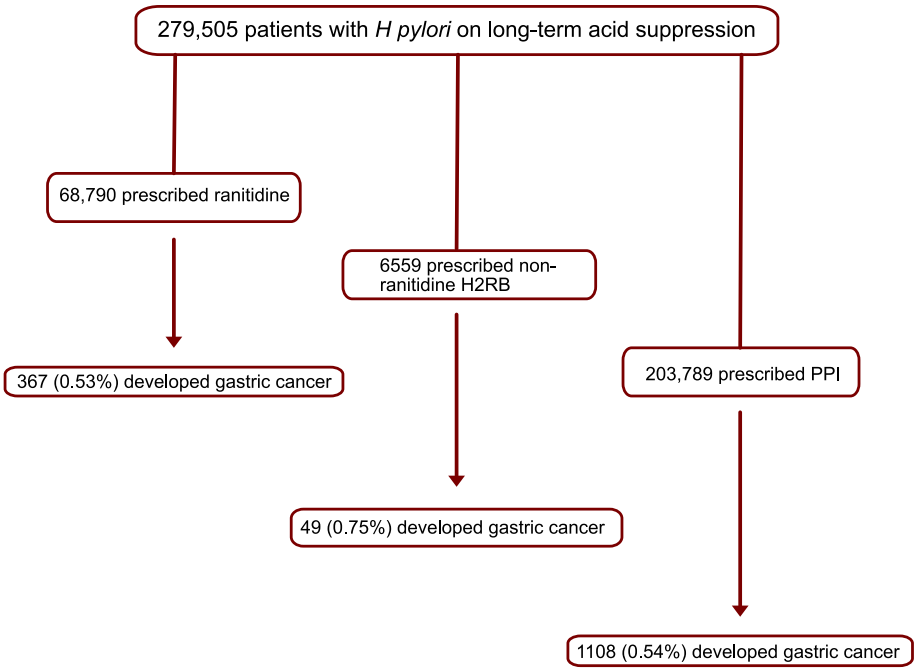


**Fig. 1** Flowchart demonstrating number of persons per acid suppressant category, and number of persons who developed gastric cancer

initially prescribed acid suppressant and future GC. Demographics associated with future cancer included increasing age (HR 1.18, 95% CI 1.15–1.20, $p < 0.001$), Hispanic or Latino ethnicity (HR 1.46, 95% CI 1.21–1.75, $p < 0.001$), race classified as Black (HR 1.89, 95% CI 1.68–2.14) or Asian (HR 2.03, 95% CI 1.17–3.52), $p < 0.001$ for race, and gender (female gender HR 0.64, 95% CI 0.48–0.85, $p = 0.02$). Smoking was also associated with future cancer (HR 1.38, 95% CI 1.23–1.54, $p < 0.001$). As compared to ranitidine, non-ranitidine H2RB users were more likely to develop future cancer (HR 1.83, 95% CI 1.36–2.48); by contrast, there was no significant different in the risk of GC between ranitidine and PPI users (HR 0.92, 95% CI 0.82–1.04) $p < 0.001$ for difference among groups. Supplemental Fig. 1 displays the cumulative hazard of GC development by category of acid suppressant prescribed, highlighting absence of differences between ranitidine- and PPI-exposed patients.

For our secondary analysis evaluating the impact of HP treatment and eradication, we identified 27,999 persons with a positive diagnostic test among the larger cohort. Of these, 5,243 (18.7%) were prescribed ranitidine, 305 (1.1%) were prescribed a non-ranitidine H2RB, and 22,451 (80.1%) were prescribed a PPI. Table 3 compares these groups. Of those who were prescribed ranitidine, 971 (18.5%) had confirmed HP eradication. Of those prescribed a non-ranitidine H2RB, 44 (14.4%) had confirmed eradication, and of those given PPIs, 4,665 (20.8%) had confirmed eradication.

Table 4 displays results of a multivariable Cox proportional hazard model evaluating the relationship between initially prescribed acid suppressant and future GC among those with a positive diagnostic test for HP (endoscopic pathology, stool antigen, urea breath test) considering treatment and eradication status. Increasing age and Black or African American race continued to be significantly associated with increased future risk of cancer. Non-ranitidine H2RBs continued to have increased risk with future GC (HR 3.97, 95% CI 1.36–11.65, $p < 0.001$ among groups), as compared to ranitidine, while PPI use was associated with no significant risk difference (HR 1.29, 95% CI 0.81–2.05). Eradication status was also significant, as compared to those with persistent infection, those with confirmed HP eradication (HR 0.24, 95% CI 0.14–0.40) or unknown eradication status (HR 0.13, 95% CI 0.08–0.21) had a decreased risk of future cancer, $p < 0.001$.

## Sensitivity Analyses

Given the finding of increased GC risk among those prescribed non-ranitidine H2RBs, we conducted further analyses to identify if any particular non-ranitidine H2RB was driving the association, if there was effect modification by eradication status, or a change over time. These are further described in the Supplement. Throughout all of these analyses, ranitidine was not associated with increased future GC risk.

**Table 2** Multivariable Cox proportional hazard model evaluating association between acid suppression and gastric cancer

| | HR (95% CI) | *p* value |
|---|---|---|
| Age[a] | 1.18 (1.15–1.20) | < 0.001 |
| Ethnicity | | < 0.001 |
| Not Hispanic or Latino | Reference | |
| Hispanic or Latino | 1.46 (1.21–1.75) | |
| Unknown | 1.64 (1.33–2.02) | |
| Race | | < 0.001 |
| White | Reference | |
| Black or African American | 1.89 (1.68–2.14) | |
| American Indian or Alaskan Native | 1.20 (0.68–2.12) | |
| Asian | 2.03 (1.17–3.52) | |
| Native Hawaiian or other Pacific Islander | 0.65 (0.33–1.31) | |
| Unknown | 1.23 (1.01–1.50) | |
| History of smoking | 1.38 (1.23–1.54) | < 0.001 |
| Female gender | 0.64 (0.48–0.85) | 0.02 |
| Poverty level of zip code where patient resided at HP diagnosis | | 0.04 |
| < 10% residing below poverty level | Reference | |
| 10–24.9% residing below poverty level | 0.82 (0.72–0.94) | |
| 25–49.9% residing below poverty level | 0.97 (0.84–1.13) | |
| ≥ 50% residing below poverty level | 1.15 (0.86–1.54) | |
| Unknown | 0.78 (0.59–1.04) | |
| Category of acid suppression | | < 0.001 |
| Ranitidine | Reference | |
| Non-ranitidine H2RB | 1.83 (1.36–2.48) | |
| PPI | 0.92 (0.82–1.04) | |

*HP H pylori*, *H2RB* histamine type 2 receptor blockers, *PPI* proton pump inhibitor

[a]Age is per 5-year incremental increase in year

## Discussion

In the largest cohort of US patients with HP prescribed an acid suppressant, we demonstrate that there is no demonstrable association of ranitidine use and future GC. As noted above, the US FDA requested withdrawal of all ranitidine drugs from the market due to concerns of higher than acceptable levels of carcinogenic contaminant. While our results certainly do not call this decision into question, they demonstrate that the true gastric carcinogenic impact of NDMA-containing ranitidine in persons in the US with HP is likely minimal to nonexistent, providing reassurance to those who have taken ranitidine.

In multivariable analysis, ranitidine use was not associated with development of future cancer, as compared to users of other acid suppressants (including PPIs and other H2RBs). Even when adjusting for HP eradication, the most important modifiable risk factor in gastric carcinogenesis, ranitidine use was not associated with GC. Risk factors for GC in our cohort included known risk factors, that have been previously reported in this cohort and in other studies. These include increasing age, racial and ethnic minority status, male gender, and smoking [15, 29–38]. In time-specific analyses, there was no period in which ranitidine was associated with future GC, suggesting there is no discernable difference in formulation of the medication over time.

Ranitidine is not the first medication to be associated with NDMA contamination. NDMA has also been found in common hypertension medications, such as valsartan [3]. A 2016 Danish cohort study evaluated the association between NDMA-contaminated valsartan and future cancer risk and found no increased short-term cancer risk, though they noted nonsignificant increased risks for colorectal and uterine cancers [4]. Similar to that study, our present study, while reassuring, does not yet fully inform on long-term risk.

In our cohort, PPIs were not significantly associated with future GC. There have been numerous studies throughout the years attempting to elucidate the relationship between PPIs and GC. Theoretically, PPIs could be associated with lower risk, as they are associated with reduced mucosal injury, inflammation, and regeneration and may histologically suppress HP [39–41]. Yet many studies have found that acid suppression is associated with future GC [10, 42, 43]. These studies are considered markedly prone to confounding by indication and protopathic bias. In one study, the positive association between acid suppression and GC was limited to those with ulcer disease, suggesting that the indication for the medication is a risk factor, not the medication itself [44]. A controversial 2018 study from Hong Kong evaluating the risk of GC development in patients prescribed HP treatment and long-term acid suppressants concluded that long-term PPI use was associated with increased GC risk even after HP treatment [9, 11]. In response, the Canadian Association of Gastroenterology issued a statement questioning the validity and conclusions of the study, and stating that "physicians should not change practice in their use of PPIs based on the stated conclusions of this study" [45]. When we conducted sensitivity analyses restricted to particular time periods, we also demonstrated that early on, when PPIs were less popular, they were associated with increased GC risk. This is likely confounding by indication, as those persons prescribed PPIs at that time had a strong clinical indication [46]. We believe that our findings in our larger cohort, which show that PPI use is not associated with GC among patients with HP prescribed long-term acid suppressants, are not only consistent with clinical guidance, but methodologically valid, as we utilized a cohort with a defined risk factor, clinical indication for long-term acid suppression, and adjusted for critical confounders such as eradication status of HP.

An unexpected finding was that non-ranitidine H2RBs appeared to be associated with an increased risk of GC.

**Table 3** Comparison of patients treated for *H pylori* after positive diagnostic test by acid suppressant medication

| | Ranitidine ($n = 5243$) | Non-ranitidine H2RB ($n = 305$) | PPI ($n = 22{,}451$) | $p$ value |
|---|---|---|---|---|
| Age at HP diagnosis, median (IQR) | 63.4 (55.6, 70.8) | 65.9 (58.7, 76.2) | 61.6 (53.2, 68.6) | < 0.001 |
| Male (%) | 4890 (93.3%) | 290 (95.1%) | 20,741 (92.4%) | 0.02 |
| Race | | | | < 0.001 |
| White | 2542 (48.5%) | 147 (48.2%) | 10,145 (45.2%) | |
| Black or African American | 1536 (29.3%) | 67 (22.0%) | 7420 (33.0%) | |
| American Indian or Alaskan Native | 46 (0.9%) | 0 (0.0%) | 185 (0.8%) | |
| Asian | 20 (0.4%) | 0 (0.0%) | 138 (0.6%) | |
| Native Hawaiian or other Pacific Islander | 46 (0.9%) | 1 (0.3%) | 198 (0.9%) | |
| Unknown | 1053 (20.1%) | 90 (29.5%) | 4365 (19.4%) | |
| Ethnicity | | | | < 0.001 |
| Not Hispanic / Latino | 3635 (69.3%) | 187 (61.3%) | 16,146 (71.9%) | |
| Hispanic or Latino | 739 (14.1%) | 21 (6.9%) | 2589 (11.5%) | |
| Unknown | 869 (16.6%) | 97 (31.8%) | 3716 (16.6%) | |
| Ever smoker (%) | 1573 (30.0%) | 83 (27.2%) | 6384 (28.4%) | 0.07 |
| Poverty level of zip code where patient resided at HP diagnosis | | | | < 0.001 |
| < 10% residing below poverty level | 890 (17.0%) | 58 (19.0%) | 4721 (21.0%) | |
| 10–24.9% residing below poverty level | 2394 (45.7%) | 143 (46.9%) | 10,625 (47.3%) | |
| 25–49.9% residing below poverty level | 1438 (27.4%) | 87 (28.5%) | 5570 (24.8%) | |
| ≥ 50% residing below poverty level | 248 (4.7%) | 5 (1.6%) | 591 (2.6%) | |
| Unknown | 273 (5.2%) | 12 (3.9%) | 944 (4.2%) | |
| Method of HP diagnosis | | | | < 0.001 |
| Pathology | 3704 (70.6%) | 201 (65.9%) | 17,300 (77.1%) | |
| Stool Antigen | 1487 (28.4%) | 99 (32.5%) | 4985 (22.2%) | |
| Urea Breath Test | 52 (1.0%) | 5 (1.6%) | 166 (0.7%) | |
| Treated for HP diagnosis within VHA | 3942 (75.2%) | 201 (65.9%) | 17,644 (78.6%) | < 0.001 |
| HP eradication status | | | | < 0.001 |
| Not eradicated | 101 (1.9%) | 3 (1.0%) | 518 (2.3%) | |
| Eradicated | 971 (18.5%) | 44 (14.4%) | 4665 (20.8%) | |
| Unknown | 4171 (79.6%) | 258 (84.6%) | 17,268 (76.9%) | |
| Category of second medication, if patient switched after first | | | | < 0.001 |
| Ranitidine | – | 103 (40.9%) | 3018 (91.9%) | |
| Non-ranitidine H2RB | 101 (2.4%) | – | 265 (8.1%) | |
| PPI | 4037 (97.6%) | 149 (59.1%) | – | |
| Develop nonproximal gastric adenocarcinoma | 21 (0.4%) | 4 (1.3%) | 128 (0.6%) | 0.06 |

*HP H pylori*, *H2RB* histamine type 2 receptor blockers, *ICD* International Classification of Diseases, *PPI* proton pump inhibitor, *VHA* Veterans Health Administration

These H2RBs have not been withdrawn from market and are not known to contain NDMA; thus, this finding was unexpected. To investigate this further, we conducted sensitivity analyses to identify any potential characteristics of patients who were taking these non-ranitidine H2RBs. Among the various non-ranitidine H2RBs, we found that the HR for increased future GC risk was similar. We compared non-ranitidine H2RBs to ranitidine and PPI users (Table 1) and found that non-ranitidine H2RB users were older and more likely male. They were more likely to have unknown race and ethnicity listed, and less likely to be classified as smokers. They were less likely to be diagnosed by endoscopic pathology and stool antigen. We then evaluated to see if there were any differences among H2RB users who switched to a second acid suppressant agents. We found that among ranitidine users who switched to a second antacid suppressant (perhaps due to persistent symptomatology), 97.4% switched to a PPI. Among non-ranitidine H2RB users who switched, only 52.2% switched to a PPI. Given these findings, we believe there is some inherent difference in those patients who were prescribed non-ranitidine H2RBs, as they were less likely to be diagnosed with true diagnostic

**Table 4** Multivariable Cox proportional hazard model evaluating association between acid suppression and gastric cancer by eradication status

| | HR (95% CI) | *p* value |
|---|---|---|
| Age[a] | 1.25 (1.16–1.35) | < 0.001 |
| Race | | 0.03 |
| White | Reference | |
| Black or African American | 1.45 (1.04–2.03) | |
| American Indian or Alaskan Native | * | |
| Asian | 1.69 (0.23–12.18) | |
| Native Hawaiian or other Pacific Islander | 0.81 (0.11–5.84) | |
| Unknown | 0.34 (0.17–0.68) | |
| History of smoking | 1.33 (0.95–1.85) | 0.09 |
| Acid suppressant | | 0.04 |
| Ranitidine | Reference | |
| Non-ranitidine H2RB | 3.97 (1.36–11.65) | |
| PPI | 1.29 (0.81–2.05) | |
| Eradication status of HP | | < 0.001 |
| Persistent infection | Reference | |
| Confirmed eradication of HP | 0.24 (0.14–0.40) | |
| Unknown HP eradication status | 0.13 (0.08–0.21) | |

Other factors evaluated but not included in the final model due to nonsignificance included ethnicity, gender, poverty level, and whether they received treatment for HP within the VHA

*HP H pylori*, *H2RB* histamine type 2 receptor blockers, *PPI* proton pump inhibitor

[a]Age is per 5-year incremental increase in year

*$< 1^{-10}$

testing, less likely to have documented racial and ethnic categories (and perhaps some misclassification of smoking), and even when symptoms may have persisted, did not switch to the "strongest" acid suppressant, PPIs. This could represent a source of confounding. In addition to patient characteristics, we evaluated time periods. In sensitivity analyses evaluating specific time periods, non-ranitidine H2RB use decreased markedly over time, with the introduction and popularity of PPIs (as well as the continued popularity of ranitidine) [1, 46]. In those multivariable models, it is only in the 1998–2002 period where H2RBs are associated with future GC, though the HR is similar to PPIs. As we note above, this is likely more reflective of confounding by indication. Overall smaller sample sizes of non-ranitidine H2RB users also likely impacts estimates. Though we were unable to elucidate the reason behind these findings, another study also found that famotidine, a non-ranitidine H2RB, was associated with high cancer incidence than ranitidine, using a large nationwide database [47, 48]. Further studies are needed to elucidate this finding and provide mechanistic insight, but nonetheless, our findings only strengthen the evidence for the lack of association of ranitidine and GC.

There are several limitations to this study. The retrospective nature diminishes the ability to determine causality. We are unable to determine on an individual level the amount of NDMA consumed, or particular dose–response relationships stemming from the amount of NDMA contaminant (i.e., duration or dosage). That we used an HP cohort has some inherent selection bias (HP is only tested for due to a clinical indication), and we are unable to compare to it a confirmed background or control population without HP. However, controlling for HP status is of utmost importance in determining the association of ranitidine and GC. We believe using a retrospective cohort with a large sample size and granular data was the best approach to answer this question. A long-term randomized control trial to address this question is not feasible or ethical, and contacting each individual patient to ascertain exposures that may have occurred over 15 years ago is similarly infeasible and subject to its own biases. Limiting it to those persons with HP prescribed a long-term acid suppressant minimizes bias among the cohort. While the GC risk could theoretically be higher in non-HP-infected individuals, epidemiology of GC in the USA suggests that the impact would be negligible. That we used the VHA limits the generalizability of the study somewhat, as it is a predominantly male (> 90%) veteran population, and not necessarily representative of the demographics of the USA. However, in a previously published study using the same cohort, we identified that compared to persistent HP infection, eradication of HP had a SHR of 0.24 (95% CI 0.15–0.41, $p < 0.001$) for future nonproximal gastric adenocarcinoma [15]. A recently published randomized control trial evaluating the impact of HP eradication among those at high risk of GC found a near-identical point estimate (HR 0.27; 95% CI 0.10–0.70) when comparing the development of cancer in those who had persistent infection versus those who had confirmed eradication of HP [49]. This finding of real-world data providing a nearly identical point estimate for the decreased risk of GC after HP eradication provides strong evidence for the external validity of our cohort. There are also possibilities for false-negative/-positive testing. There could be measurement issues, leading to misclassification. These include patients receiving care outside the VHA, limiting available oncologic diagnoses and cancer registry inputs or HP diagnoses. However, misclassification of HP status would only affect inclusion into the cohort, and misclassification of the outcome, inadvertently including a nonproximal gastric adenocarcinoma, should not be markedly differential between the groups. That we reproduced known risk factors for nonproximal gastric adenocarcinomas (which are distinct from esophageal and proximal cancers) suggests misclassification of the outcome is minimal [50]. When evaluating eradication status, both those with confirmed HP eradication and unknown HP eradication status had a decreased risk of future cancer. Those patients with unknown eradication status may have been retested outside of the VHA, treated successfully with a

course of antibiotics (though not retested) or have some other reason to be lower risk for cancer than those persons who were tested for eradication, apart from HP. We were unable to ascertain whether patients also used acid suppressants OTC or from another health system, leading to misclassification of data. This could lead to misclassification of the exposure, but should not be differential among acid suppression categories. We are unable to incorporate symptoms due to collinearity, and so are unable to address indication for acid suppression. We further do not analyze a dose-response relationship (given the OTC nature of acid suppressants, this would be markedly susceptible to misclassification). As we note above, despite these limitations, a retrospective cohort study remains the best approach to provide estimates of future cancer risk regarding a medication that has now been withdrawn from market.

The strengths of our study are primarily related to the unique nature of the cohort, being large and granular enough to answer a pressing question about the association of ranitidine and GC. Using the largest and most comprehensive US database, we are able to compare GC risk among patients with HP who were prescribed acid suppressants. Comparison of these groups demonstrates that ranitidine is not demonstrably associated with future GC as compared to other acid suppressants. Other, previously described risks, demographics, smoking, and HP eradication, remain important in future gastric carcinogenesis. Our follow-up time was similar to other recent pharmacoepidemiologic studies investigating contaminant and future cancer risk, but, as in those studies, longer follow-up is necessary to confirm these findings [4, 51].

## Conclusion

On a population level, among patients with HP, the most important risk factor for GC, ranitidine was not associated with any difference in future GC risk.

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**Author's contribution** SK contributed to study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and statistical analysis. DSG contributed to study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision. DEK contributed to study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision.

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## Declarations

**Conflict of interest** SK: Education Conference (Boston Scientific Corporation, Olympus Corporation). DSG: Research grant support (Gilead, Merck, AbbVie, Zydus). DEK: Research grant support (Gilead, Bayer).

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. The Institutional Review Board of the Corporal Michael J. Crescenz VA Medical Center approved this study.

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