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ORIGINAL RESEARCH ARTICLE

Risk of Cancer in Association with Ranitidine and Nizatidine vs Other H2 Blockers: Analysis of the Japan Medical Data Center Claims Database 2005–2018

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Abstract

Introduction In September 2019, ranitidine and nizatidine were suggested to contain *N*-nitrosodimethylamine, a carcinogenic substance. People have since been concerned about the potential impact of ranitidine/nizatidine use on the risk of cancer.

Objective The objective of this study was to investigate the risk of cancer among people receiving ranitidine or nizatidine compared with other histamine 2 receptor antagonists (H2 blockers) [cimetidine, famotidine, roxatidine, and lafutidine].

Methods In the Japan Medical Data Center claims database (comprising people aged < 75 years) from 2005 to 2018, we identified new adult users of H2 blockers and classified them into ranitidine/nizatidine users and other H2 blocker users. We estimated the incidence of cancer diagnosis in each group and conducted a multivariable Cox regression analysis.

Results We identified 113,745 new users of ranitidine/nizatidine (median age 41.2 years [interquartile range 31.7–51.1]; 49.1% men; median follow-up 2.4 years [1.1–4.5]) and 503,982 new users of other H2 blockers (median age 40.9 years [31.1–51.2]; 51.0% men; median follow-up 2.3 years [0.9–4.2]). The incidence rate of cancer diagnosis was 6.39 (95% confidence interval 6.13–6.66) cases per 1000 person-years (top three sites: breast 14.8%; colorectal 14.6%; and stomach 11.5%) in the ranitidine/nizatidine group and 6.17 (6.05–6.30) cases per 1000 person-years (colorectal 14.7%; breast 13.5%; and stomach 11.2%) in the other H2 blockers group. The adjusted hazard ratio (ranitidine/nizatidine users vs other H2 blocker users) was 1.02 (0.98–1.07). The results were similar by follow-up length, by cancer site, and when ranitidine and nizatidine users were separately compared with the other H2 blockers group. By cumulative dose, the adjusted hazard ratio (95% confidence interval) was 1.03 (0.98–1.08) from 1 to 180 defined daily doses (DDDs), 1.00 (0.73–1.39) from 181 to 365 DDDs, 0.95 (0.61–1.48) from 366 to 730 DDDs, and 0.83 (0.45–1.55) at > 730 DDDs.

Conclusions We found no evidence that ranitidine/nizatidine is associated with an increased risk of cancer, although further studies with more accurate measurement of exposure, inclusion of older people, and longer follow-up may be needed.

1 Introduction

Histamine 2 receptor antagonists (H2 blockers) have been used to treat peptic ulcers, gastritis, and reflux esophagitis. In September 2019, the European Medicines Agency and US Food and Drug Administration announced that ranitidine hydrochloride contains *N*-nitrosodimethylamine (NDMA) [1–3], which is "probably carcinogenic to humans (group 2A)" according to the International Agency for Research on Cancer [4]. The Japanese Ministry of Health, Labour and Welfare responded to this statement by asking domestic suppliers to analyze their products [5], and NDMA was indeed detected in ranitidine as well as in nizatidine, the chemical formula of which is similar to that of ranitidine [6]. Consequently, all ranitidine products (including tablets and injectable formulations) were recalled from the market in Japan [7], as in the USA and Europe [8–12].

Sensational reporting of these incidents by the media has since raised concern about the risk of cancer in association with previous ranitidine/nizatidine use [13]. Thus, from a public health perspective, it is important to promptly investigate the risk of cancer associated with ranitidine and

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Key Points

In the Japan Medical Data Center claims database (comprising employed workers in medium- to large-scale companies and their family members aged < 75 years) from 2005 to 2018, we found no evidence of an increased risk of cancer among people receiving ranitidine or nizatidine (which have been suggested to contain *N*-nitrosodimethylamine, a carcinogenic substance) compared with people receiving other histamine 2 receptor antagonists.

The results of this study may alleviate concerns about a potential risk of cancer in people exposed to ranitidine/nizatidine, although assessment with more accurate measurement of the exposure level, inclusion of older people, and longer follow-up may be warranted.

nizatidine using the best available data accumulated to date. To our knowledge, no study on this issue has been published from any country. Therefore, using a Japanese large database of company employees and their family members from 2005 to 2018, we investigated the risk of cancer among people receiving ranitidine or nizatidine compared with other H2 blockers as an active comparator.

2 Methods

2.1 Data Source

We used a commercially available, administrative claims database from the Japan Medical Data Center (JMDC) Co., Ltd. (Tokyo, Japan), which has been used for pharmacoepidemiological research [14, 15]. The JMDC claims database has been collecting outpatient, inpatient, and pharmacy claims data from health insurance associations for employed workers in medium- to large-scale companies and their family members (within the third degree of kinship) since January 2005. By August 2018 (the end of the study period for the current study), the cumulative observed population reached nearly 5.7 million. In August 2018, there were around 3.65 million active patients registered in the database, accounting for nearly 3% of the Japanese population in 2018. The upper age limit in the JMDC database is 75 years because this database does not cover claims from the Medical Care System for the Advanced Elderly, which is available for everyone aged ≥ 75 years in the current Japanese healthcare system. In addition to demographics and information on eligibility, the JMDC database also includes monthly data on prescribed and dispensed medications (in both hospitals and clinics) coded using the World Health Organization Anatomical Therapeutic Chemical (ATC) classifications [16], as well as inpatient and outpatient diagnoses recorded based on the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes [17]. A list of all codes used in the current study to define the exposure, outcome, and covariates is shown in the Electronic Supplementary Material (ESM) 1.

This study was approved by the Institutional Review Board of The University of Tokyo. The need for informed consent was waived because of the anonymous nature of the data. Patient privacy and confidentiality were preserved because each individual's identifier was removed at the time of the database creation.

2.2 Study Population

In the JMDC database, we first identified all patients who received any type of H2 blocker (including tablets and injectable formulations) available in Japan, including ranitidine, nizatidine, cimetidine, famotidine, roxatidine, and lafutidine, from January 2005 to August 2018. We then excluded patients who had been prescribed H2 blockers during the first 6 months after registration to the database because they were likely to be prevalent users with unknown cumulative doses and lengths of H2 blocker therapy. We also excluded patients aged < 18 years at the time of new prescription of H2 blockers and patients with a history of cancer, defined as any cancer diagnosis recoded before or within the same month as a new prescription of H2 blockers.

2.3 Exposure Definition and Follow-Up

The exposure of interest was the use of ranitidine and nizatidine. At the time of the new prescription of H2 blockers in the JMDC database, we divided the study participants into two groups: the ranitidine/nizatidine group and the other H2 blockers group. They were followed up until the incidence of new cancer diagnosis, withdrawal from the JMDC database for any reason (including death and disqualification from health insurance), or the end of the study period (31 August, 2018). Additionally, to address the time-dependent exposure status while avoiding immortal time bias [18], if a patient in the other H2 blockers group subsequently received ranitidine or nizatidine during follow-up, the patient was censored from the other H2 blockers group and included in the ranitidine/nizatidine group as a new user of ranitidine/nizatidine from that timepoint forward. However, once a patient had been allocated to the ranitidine/nizatidine group, he or she stayed in that group even if other H2 blockers were

subsequently prescribed under the assumption that patients once exposed to ranitidine/nizatidine could be at risk of developing cancer in association with ranitidine/nizatidine. A graphical depiction of representative patients used to classify the exposure status is shown in ESM 2.

2.4 Outcome Definition

The outcome of interest was the first cancer diagnosis (excluding non-melanoma skin cancer) in the JMDC database, defined as ICD-10 codes C00–C96 (excluding C44). We also assessed the cancer category at the time of the first cancer diagnosis according to the ICD-10 code classification (ESM 1) used in a recent study [19]: colorectal cancer, pancreatic cancer, lung cancer, malignant melanoma, breast cancer, uterine cancer, prostate cancer, kidney cancer, and bladder cancer. Additionally, we created a category of gastric cancer because H2 blockers are mainly prescribed for gastric symptoms. We therefore considered that the potential link between H2 blockers and gastric cancer should be specifically examined. Other cancers were grouped.

To our knowledge, two validation studies on cancer have been performed using Japanese claims data [20, 21]. One validation study on any cancer diagnosis among hospitalized patients showed a sensitivity of 83.5% and a specificity of 97.7% [20]. The other validation study on breast cancer diagnosis showed a sensitivity of 98.7% and specificity of 99.3% [21].

2.5 Covariates

We considered that the main confounding factor was an indication for an H2 blocker. Such indications included peptic ulcer disease, gastritis, and reflux esophagitis, which could affect both the choice of H2 blocker and the incidence of certain cancer types (such as gastric and esophageal cancers). Additionally, with reference to a recent study investigating the association between NDMA-contaminated valsartan (an angiotensin II receptor blocker) and the risk of cancer [19], we adjusted for covariates that potentially affect the incidence of cancer: age; sex; co-medications including low-dose aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, selective serotonin reuptake inhibitors, and proton pump inhibitors; comorbidities including diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and alcohol-related disease; and the Charlson Comorbidity Index [22]. These covariates were defined at the start of follow-up in the ranitidine/nizatidine group and other H2 blockers group based on the ATC and ICD-10 codes (ESM 1) recorded within the past 6 months. The covariates of patients who started other H2 blockers and subsequently received ranitidine or nizatidine were redefined when the patients were included in the ranitidine/nizatidine group as new users.

2.6 Statistical Analysis

We compared the baseline characteristics of patients between the ranitidine/nizatidine group and the other H2 blockers group using standardized differences between the groups instead of *p*-values. This is because *p*-values largely depend on the study sample size (and thus many factors resulted in a *p* value of <0.001 in the current study because of its large sample size), while the standardized difference reflects the actual difference between the groups regardless of the sample size. We then estimated the incidence rate of cancer diagnosis and demonstrated the breakdown of the cancer diagnosis category in each group. We conducted univariable and multivariable Cox regression analyses to compare the hazard for cancer diagnosis between the two groups. In addition to the calendar year at the start of follow-up, all the aforementioned covariates were adjusted in the multivariable Cox regression model. To account for a potential intra-person correlation because of the fact that patients initially included in the other H2 blockers group could be subsequently included in the ranitidine/nizatidine group as new patients, we used robust standard errors to adjust for clustering by the unique patient identifier variable [23].

We conducted several sensitivity analyses. First, we started the patient follow-up at 1 year after the first prescription, considering some induction and latent periods between exposure to ranitidine/nizatidine and identification of cancer [24]. Patients with follow-ups of <1 year were naturally excluded from this analysis. Second, in the ranitidine/nizatidine group, we excluded patients starting other H2 blockers and subsequently switching to ranitidine/nizatidine because they may have been systematically different from those starting therapy with ranitidine/nizatidine. Third, we defined the outcome as a cancer diagnosis with chemotherapy (recorded as ATC code L01 for inpatient or outpatient treatment), radiotherapy (procedure codes M000–M004), or hormone therapy for cancer (ATC code L02). The definition of cancer with records of cancer-specific treatments is expected to be more specific (although it may be less sensitive) than cancer diagnosis codes only [21]. The JMDC database does not provide information on the pathological diagnosis of cancer or cancer stage.

In additional analyses, to further clarify the relationship between ranitidine/nizatidine and cancer, we compared the ranitidine/nizatidine group and the other H2 blockers group by cumulative dose, follow-up length, and cancer site. The first analysis by cumulative dose was conducted to examine a potential dose–response relationship between ranitidine/nizatidine and cancer diagnosis. For this analysis, according to the cumulative dose since the first prescription, we

split the patient follow-up period into four intervals: 1–180 defined daily doses (DDDs), 181–365 DDDs, 366–730 DDDs, and > 730 DDDs. As proposed by the World Health Organization, one DDD for comparison of different drugs is 300 mg/day for ranitidine, 300 mg/day for nizatidine, 800 mg/day for cimetidine, 40 mg/day for famotidine, 150 mg/day for roxatidine, and 20 mg/day for lafutidine [16]. For example, 365 DDDs of ranitidine corresponds to 300 mg/day (i.e., 1 DDD) for 365 days as the total number of days for which the drug was prescribed in the JMDC database. We compared the two groups (i.e., ranitidine/nizatidine group vs other H2 blockers group) for the same intervals (i.e., 1–180, 181–365, 366–730, and > 730 DDDs). If a dose–response relationship exists between ranitidine/nizatidine and cancer diagnosis, the hazard ratio should be higher in the higher cumulative dose category. Second, we compared the ranitidine/nizatidine group and the other H2 blockers group by follow-up length during the first 5 years of prescription and beyond 5 years after the first prescription. To compare the two groups during the first 5 years, patients were censored at 5 years after the first prescription. To compare the two groups beyond 5 years, we restarted the patient follow-up at 5 years after the first prescription, meaning that patients with a follow-up of < 5 years were excluded from the analysis. Finally, to compare the two groups by cancer site, we did not censor patients at the time of diagnosis of cancers other than the cancer of interest. For breast cancer, the analysis was restricted to women because only a very small number of men had a breast cancer diagnosis and the Cox regression model did not converge if men were included. Finally, we differentiated patients receiving ranitidine and nizatidine in the ranitidine/nizatidine group and compared each to the patients in the other H2 blockers group. Patients receiving both ranitidine and nizatidine during follow-up were excluded from this analysis. All statistical analyses were performed using STATA Version 16 (StataCorp, College Station, TX, USA).

3 Results

We identified 600,321 new adult users of H2 blockers in the JMDC database, comprising 96,339 patients starting ranitidine or nizatidine and 503,982 patients starting other H2 blockers (Fig. 1). Of the 503,982 patients, 17,406 patients subsequently started ranitidine/nizatidine and were therefore included in the ranitidine/nizatidine group as new users of ranitidine/nizatidine from that timepoint forward. Thus, a comparison was made between 113,745 new users of ranitidine/nizatidine (median age 41.2 years; interquartile range [IQR] 31.7–51.1 years; full range 18–74 years; 49.1% men; median follow-up 2.4 years; IQR 1.1–4.5 years) and 503,982 new users of other H2 blockers

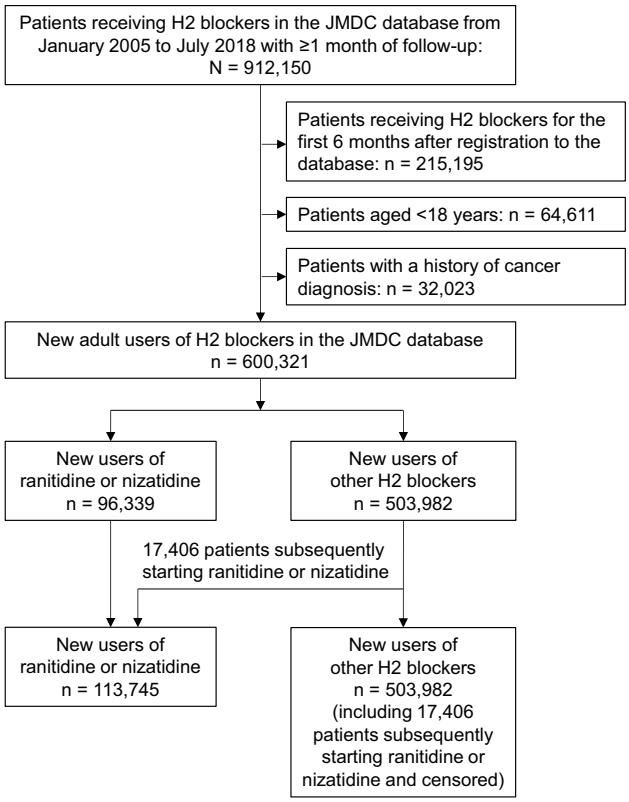

Fig. 1 Study flow chart. *H2 blockers* histamine 2 receptor antagonists, *JMDC* Japan Medical Data Center

(median age 40.9 years; IQR 31.1–51.2 years; full range 18–74 years; 51.0% men; median follow-up 2.3 years; IQR 0.9–4.2 years). The baseline characteristics were similar between the groups with the exception of reflux esophagitis (24.0% in the ranitidine/nizatidine group vs 18.2% in the other H2 blockers group) with a standardized difference of > 0.1 between the groups (Table 1). In the ranitidine/nizatidine group, there were some differences in the characteristics between purely new users of ranitidine or nizatidine ($n = 96{,}339$) and switchers from other H2 blockers to ranitidine or nizatidine ($n = 17{,}406$) [ESM 3].

We identified 270,984 prescriptions (120,509 for ranitidine, 150,475 for nizatidine) in the ranitidine/nizatidine group (median DDDs, 6; IQR 3–14) and 1,482,150 prescriptions (109,572 for cimetidine, 1,159,323 for famotidine, 33,376 for roxatidine, 179,879 for lafutidine) in the other H2 blockers group (median DDDs 6; IQR 3–14). The median prescribed daily dose was 150 mg/day (0.5 DDD; IQR 150–300 mg/day) for ranitidine, 150 mg/day (0.5 DDD; IQR 150–300 mg/day) for nizatidine, 400 mg/day (0.5 DDD; IQR 400–600 mg/day) for cimetidine, 20 mg/day (0.5 DDD; IQR 0.5–1 mg/day) for famotidine, 150 mg/day (1 DDD; IQR 75–150 mg/day) for roxatidine, and 20 mg/day (1 DDD; IQR 10–20 mg/day) for lafutidine.

Table 1 Baseline characteristics of new users of ranitidine or nizatidine and other histamine 2 receptor antagonists (H2 blockers)

	New users of ranitidine or nizatidine $N = 113,745$	New users of other H2 blockers $N = 503,982$	Standardized difference
Age, years	41.2 [31.7–51.1]	40.9 [31.1–51.2]	< 0.001
Age group, years			
18–29	23,803 (20.9)	112,475 (22.3)	0.034
30–39	29,224 (25.7)	127,137 (25.2)	0.011
40–49	29,298 (25.8)	125,184 (24.8)	0.021
50–59	21,498 (18.9)	94,001 (18.7)	0.006
60–69	8754 (7.7)	39,856 (7.9)	0.008
70–74	1168 (1.0)	5329 (1.1)	0.003
Male sex	55,843 (49.1)	256,932 (51.0)	0.038
Indications[a]			
Peptic ulcer disease	34,015 (29.9)	136,865 (27.2)	0.061
Gastritis	78,042 (68.6)	331,751 (65.8)	0.059
Reflux esophagitis	27,298 (24.0)	91,839 (18.2)	0.142
Co-medications			
Low-dose aspirin	1440 (1.3)	8132 (1.6)	0.029
NSAIDs	25,227 (22.2)	109,457 (21.7)	0.011
5-α reductase inhibitors	67 (0.1)	301 (0.1)	< 0.001
Statins	7085 (6.2)	31,495 (6.3)	0.001
Spironolactone	288 (0.3)	1402 (0.3)	0.005
Oral steroids	19,862 (17.5)	101,325 (20.1)	0.068
Hormone replacement therapy	2721 (2.4)	10,903 (2.2)	0.015
SSRIs	2893 (2.5)	11,863 (2.4)	0.012
Proton pump inhibitors	15,128 (13.3)	57,746 (11.5)	0.056
Comorbidities			
Diabetes mellitus	2890 (2.5)	14,214 (2.8)	0.017
COPD	83 (0.1)	552 (0.1)	0.012
Heart failure	2026 (1.8)	9883 (2.0)	0.013
Alcohol-related disease	417 (0.4)	2172 (0.4)	0.010
CCI score category[b]			
0	84,054 (73.9)	379,785 (75.4)	0.034
1	17,310 (15.2)	73,851 (14.7)	0.016
2	8830 (7.8)	35,215 (7.0)	0.030
≥ 3	3551 (3.1)	15,131 (3.0)	0.007

Data are presented as median [interquartile range] or *n* (%)

CCI Charlson Comorbidity Index, *COPD* chronic obstructive pulmonary disease, *NSAIDs* non-aspirin non-steroidal anti-inflammatory drugs, *SSRIs* selective serotonin reuptake inhibitors

[a]Some patients had several indications

[b]The CCI is based on diagnoses of chronic pulmonary disease (1 point), rheumatic disease (1 point), diabetes with chronic complications (1 point), renal disease (1 point), congestive heart failure (2 points), dementia (2 points), mild liver disease (2 points), hemiplegia or paraplegia (2 points), any malignancy, including lymphoma and leukemia but excluding malignant neoplasm of the skin (2 points), moderate or severe liver disease (4 points), acquired immunodeficiency syndrome/human immunodeficiency virus (4 points), and metastatic solid tumors (6 points). Notably, no patients had cancer at baseline because this was one of the exclusion criteria

There were 2289 and 9038 cases of incident cancer, resulting in an incidence rate of 6.39 (95% confidence interval [CI] 6.13–6.66) and 6.17 (95% CI 6.05–6.30) cases per 1000 person-years in the ranitidine/nizatidine group and other H2 blockers group, respectively. The median age (IQR) of patients with incident cancer diagnosis was 53.0 (44.9–60.0) years in the ranitidine/nizatidine group and 53.5 (45.4–60.8) years in the other H2 blockers group. The

breakdown of cancer sites was similar between the groups (Table 2): the top three sites were breast (14.8%), colorectal (14.6%), and stomach (11.5%) in the ranitidine/nizatidine group and colorectal (14.7%), breast (13.5%), and stomach (11.2%) in the other H2 blockers group. The proportions of patients who died, were disqualified from insurance, and were censored at the end of the study period (August 2018) were similar between the groups (ESM 4).

The crude and adjusted hazard ratios (ranitidine/nizatidine users vs other H2 blocker users) were 1.05 (95% CI 1.00–1.09) and 1.02 (95% CI 0.98–1.07), respectively (Table 3). Similar results were obtained in sensitivity analyses (1) in which follow-up started 1 year after the first prescription (adjusted hazard ratio 1.00; 95% CI 0.94–1.06), (2) that excluded 17,406 patients starting other H2 blockers and switching to ranitidine/nizatidine from the ranitidine/nizatidine group (adjusted hazard ratio 1.02; 95% CI 0.97–1.07), and (3) in which the outcome was defined as a cancer diagnosis with chemotherapy, radiotherapy, or hormone therapy for cancer (adjusted hazard ratio 1.08; 95% CI 1.00–1.16).

The results were also similar in additional analyses (Table 3). By cumulative dose, the adjusted hazard ratio (95% CI) was 1.03 (0.98–1.08) from 1 to 180 DDDs, 1.00 (0.73–1.39) from 181 to 365 DDDs, 0.95 (0.61–1.48) from 366 to 730 DDDs, and 0.83 (0.45–1.55) at > 730 DDDs. By follow-up length, the adjusted hazard ratio (95% CI) was 1.03 (0.98–1.08) during the first 5 years and 0.97 (0.85–1.11) beyond 5 years after the first prescription. By cancer site, the adjusted hazard ratio (95% CI) was 1.04 (0.92–1.17) for breast cancer, 1.02 (0.91–1.15) for colorectal cancer, and 1.09 (0.96–1.24) for gastric cancer. Finally, after differentiating patients in the ranitidine/nizatidine group, the adjusted hazard ratio (95% CI) was 1.01 (0.95–1.08) for ranitidine users and 0.98 (0.92–1.04) for nizatidine users compared with the other H2 blockers group.

4 Discussion

In this study using a large Japanese contemporary database of routinely collected administrative claims data from 2005 to 2018, we found no evidence of an increased risk of cancer diagnosis in people receiving ranitidine and nizatidine compared with people receiving other H2 blockers. The results were similar in several sensitivity and additional analyses, notably among people with larger cumulative doses.

Previous basic studies have suggested that NDMA can cause cancer in animals [25, 26]. In humans, observational studies have suggested that higher intake of foods containing NDMA may be associated with an increased risk of developing cancers such as gastric and colorectal cancers [27–29]. In 2018, valsartan (an angiotensin II receptor blocker) manufactured at a Chinese facility was found to be contaminated by NDMA [30]. A Danish nationwide study investigated the risk of cancer between patients receiving the NDMA-contaminated valsartan and those receiving valsartan manufactured at other facilities from 2012 to 2018 [19]. The study did not identify a statistically significant difference in the risk of cancer between the groups, with an adjusted hazard ratio (NDMA exposed vs not exposed) of 1.09 (95% CI 0.85–1.41) for overall cancer.

However, the results of the Danish study on valsartan are unlikely to help mitigate concerns about the potential risk of cancer associated with NDMA-contaminated ranitidine and nizatidine, mainly because the backgrounds of people taking antihypertensives and those taking H2 blockers are different.

Table 2 Breakdown of cancer diagnosis categories

Cancer diagnosis category (ICD-10 codes)	No. of outcomes among 113,745 new users of ranitidine or nizatidine	%	No. of outcomes among 503,982 new users of other H2 blockers	%
Any cancer (C00–C96, excluding C44)	2289	100	9038	100
Cancer diagnosis category				
Gastric cancer (C16)	263	11.5	1011	11.2
Colorectal cancer (C18–C20)	334	14.6	1333	14.7
Pancreatic cancer (C25)	93	4.1	432	4.8
Lung cancer (C34)	155	6.8	650	7.2
Malignant melanoma (C43)	7	0.3	53	0.6
Breast cancer (C50)	338	14.8	1222	13.5
Uterine cancer (C54–C55)	93	4.1	348	3.9
Prostate cancer (C61)	116	5.1	485	5.4
Kidney cancer (C64)	55	2.4	188	2.1
Bladder cancer (C67)	53	2.3	212	2.4
Other cancers	782	34.2	3104	34.3

H2 blockers histamine 2 receptor antagonists, *ICD-10 codes* International Classification of Diseases, 10th Revision codes

Table 3 Incidence rate of cancer diagnosis in the ranitidine or nizatidine group and other histamine 2 receptor antagonists (H2 blockers) group with hazard ratios (HRs)

	New users of ranitidine or nizatidine			New users of other H2 blockers			Crude HR (95% CI)	Adjusted HR[a] (95% CI)
	No. of outcomes/ patients	Amount of population-time of follow-up (PY)	Crude rate [/1000 PY] (95% CI)	No. of outcomes/ patients	Amount of population-time of follow-up (PY)	Crude rate [/1000 PY] (95% CI)		
Main analysis	2289/113,745	358,220	6.39 (6.13–6.66)	9038/503,982	1,464,596	6.17 (6.05–6.30)	1.05 (1.00–1.09)	1.02 (0.98–1.07)
Sensitivity analyses								
Starting follow-up at 1 year after the first prescription	1439/86,108	257,953	5.58 (5.30–5.87)	5646/368,296	1,027,341	5.50 (5.35–5.64)	1.02 (0.96–1.08)	1.00 (0.94–1.06)
Excluding people starting other H2 blockers and subsequently switching to ranitidine/nizatidine in the ranitidine/nizatidine group	1916/96,339	304,587	6.29 (6.02–6.58)	9038/503,982	1,464,596	6.17 (6.05–6.30)	1.03 (0.98–1.08)	1.02 (0.97–1.07)
Defining the outcome as a cancer diagnosis with chemotherapy, radiotherapy, or hormone therapy	894/113,745	361,497	2.47 (2.32–2.64)	3374/503,982	1,477,526	2.28 (2.21–2.36)	1.10 (1.02–1.18)	1.08 (1.00–1.16)
Additional analyses								
By cumulative dose								
During the interval of 1–180 DDDs	2207/113,745	350,446	6.05 (5.92–6.18)	8646/503,982	1,429,092	6.30 (6.04–6.57)	1.05 (1.00–1.10)	1.03 (0.98–1.08)
During the interval of 181–365 DDDs	45/2699	4616	9.75 (7.28–13.06)	197/13,382	20,285	9.71 (8.45–11.17)	1.01 (0.73–1.40)	1.00 (0.73–1.39)
During the interval of 366–730 DDDs	24/1294	2264	10.60 (7.10–15.81)	121/6406	11,117	10.88 (9.11–13.01)	0.98 (0.63–1.51)	0.95 (0.61–1.48)
During the interval of > 730 DDDs	13/491	1267	10.26 (5.96–17.67)	74/2396	5950	12.44 (9.90–15.62)	0.83 (0.46–1.50)	0.83 (0.45–1.55)

Table 3 (continued)

	New users of ranitidine or nizatidine			New users of other H2 blockers			Crude HR (95% CI)	Adjusted HR[a] (95% CI)
	No. of outcomes/ patients	Amount of population-time of follow-up (PY)	Crude rate [/1000 PY] (95% CI)	No. of outcomes/ patients	Amount of population-time of follow-up (PY)	Crude rate [/1000 PY] (95% CI)		
By follow-up length								
During 5 years after the first prescription	1989/113,745	300,580	6.62 (6.33–6.91)	7960/503,982	1,255,473	6.34 (6.20–6.48)	1.05 (1.00–1.10)	1.03 (0.98–1.08)
Beyond 5 years after the first prescription	300/23,036	57,640	5.20 (4.65–5.83)	1078/87,257	209,123	5.15 (4.86–5.47)	1.01 (0.89–1.15)	0.97 (0.85–1.11)
By cancer site (top 3 sites)								
Breast cancer[b]	341/57,902	173,018	1.97 (1.77–2.19)	1254/247,050	673,294	1.86 (1.76–1.97)	1.05 (0.93–1.19)	1.04 (0.92–1.17)
Colorectal cancer	359/113,745	362,698	0.99 (0.89–1.10)	1428/503,982	1,481,549	0.96 (0.92–1.02)	1.04 (0.92–1.16)	1.02 (0.91–1.15)
Gastric cancer	288/113,745	362,935	0.79 (0.71–0.89)	1085/503,982	1,482,392	0.73 (0.69–0.78)	1.11 (0.97–1.26)	1.09 (0.96–1.24)
Differentiating ranitidine and nizatidine users[c]								
Ranitidine users (vs other H2 blocker users)	945/46,771	150,762	6.27 (5.88–6.68)	9038/503,982	1,464,596	6.17 (6.05–6.30)	1.03 (0.96–1.10)	1.01 (0.95–1.08)
Nizatidine users (vs other H2 blocker users)	1193/64,219	193,188	6.17 (5.83–6.54)	9038/503,982	1,464,596	6.17 (6.05–6.30)	1.00 (0.95–1.07)	0.98 (0.92–1.04)

CI confidence interval, *DDDs* defined daily doses, *PY* person-years

[a]Adjusted for age, sex, indications (peptic ulcer disease, gastritis, and reflux esophagitis), co-medications (low-dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, selective serotonin reuptake inhibitors, and proton pump inhibitors), comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, heart failure, and alcohol-related disease), Charlson Comorbidity Index score category (0, 1, 2, or ≥ 3), and calendar year at the start of follow-up

[b]The analysis was restricted to women

[c]Patients receiving both ranitidine and nizatidine during follow-up ($n = 2755$) were excluded from the analysis

More specifically, people taking H2 blockers for conditions such as peptic ulcer disease and gastroesophageal reflux disease are at risk of developing upper gastrointestinal cancer [31]. Moreover, the incidence of gastric cancer has been higher in Japan than in other countries, possibly because of a higher prevalence of *Helicobacter pylori* and high-sodium Japanese foods [32]. Thus, we conducted the current study and demonstrated for the first time (to our knowledge) that there is no significant association between ranitidine/nizatidine and the incidence of cancer diagnosis.

The strengths of this study include the use of a large contemporary database of routinely collected health records, which enabled us to examine this important public health question in a timely manner. Additionally, we employed an active comparator design to compare users of different types of H2 blockers; such a comparison is less prone to indication bias than a comparison between users and non-users of ranitidine/nizatidine. We conducted several sensitivity and additional analyses to enhance the robustness of the findings in line with recent considerations for pharmacoepidemiological studies of drug–cancer associations [24].

However, several limitations of this study should be acknowledged. First, the JMDC claims database comprises people aged < 75 years, and the proportion of older people is relatively low (Table 1); this suggests that the older people in the JMDC database are not representative of the Japanese older population. In addition, the median age of patients with an incident cancer diagnosis was around 53 years in the current study, which is obviously lower than the average age of patients with cancer in Japan (even among those aged < 75 years). Therefore, the safety of ranitidine/nizatidine in older people remains unknown, and the risk of cancer incidence remains to be confirmed by future studies of older people. Additionally, the people in the JMDC database are employed workers in medium- to large-scale companies and their family members, who are probably wealthier than the average Japanese individual. Thus, the generalizability of the study findings may also be limited. Second, our outcome definition was based on recorded diagnoses, and outcome misclassification is therefore a matter of concern (although previous validation studies have suggested high sensitivity and specificity of cancer diagnosis in Japanese claims data) [20, 21]. If misclassification of cancer diagnosis was present in the JMDC claims database, we expect that this was most likely non-differential misclassification (i.e., the extent of misclassification was similar between the ranitidine/nizatidine group and the other H2 blockers group) and thus could have diluted the true association between ranitidine/nizatidine and cancer. Third, the JMDC database contains data after 2005, while H2 blockers have been used since the 20th century. By employing a new user design, we excluded prevalent users of H2 blockers (defined as patients prescribed H2 blockers for the first 6 months after registration to the database) whose cumulative doses and length of ranitidine/nizatidine use were unknown. However, it is still possible that some people in the ranitidine/nizatidine group and the other H2 blockers group received ranitidine/nizatidine before their entry into the database. If the ranitidine/nizatidine group contained many patients with previous ranitidine/nizatidine use, the observed association (adjusted hazard ratio of 1.02) might be an overestimation (meaning that the true association would be even smaller). If the other H2 blockers group contained many patients with previous ranitidine/nizatidine use (which we believe is much less likely), the observed association might be an overestimation (meaning that the true association would be > 1.02). Moreover, although the study population was large, a relatively small number of people received large cumulative doses of ranitidine/nizatidine. In one of the additional analyses, according to the cumulative dose since the first prescription, we split the patient follow-up into four intervals: 1–180, 181–365, 366–730, and > 730 DDDs. We found no dose–response relationship (i.e., larger adjusted hazard ratio in the higher cumulative dose group). However, whether an even higher cumulative dose of ranitidine/nizatidine is associated with an increased risk of cancer remains unknown mainly because of the limited sample size and statistical power. One possible explanation of the lack of association in the current study may be that few people were exposed to a high enough level of NDMA to increase the risk of cancer. Finally, because this was an observational study, unmeasured confounding factors almost certainly exist. For example, the database did not include information on lifestyle-related factors (e.g., smoking, diet, alcohol intake, and body mass index), exposure to dietary NDMA (which is probably carcinogenic to humans [27–29]), exposure to other carcinogens, or the use of over-the-counter drugs. However, it is unlikely that the frequency or level of these exposures differed between the compared groups in the active comparator design. Meanwhile, clinicians might have had different preferences for prescribing one particular H2 blocker over another, and the probability of cancer screening might have differed among clinicians. These unmeasured confounding factors could have masked a potential association between ranitidine/nizatidine and cancer diagnosis.

Our findings may provide reassurance to people concerned about the potential risk of cancer in association with ranitidine/nizatidine use, although our study cannot confirm the safety of these drugs. Repeat assessment with longer follow-up, especially among those with a high cumulative dose, may be warranted. However, researchers using future data must account for detection/surveillance bias because

people previously exposed to ranitidine/nizatidine may be more likely to seek screening after the press announcements on the detection of NDMA in ranitidine and nizatidine released in September 2019.

5 Conclusions

In this study using a large Japanese contemporary database of routinely collected administrative claims data from 2005 to 2018, we found no evidence of an increased risk of cancer in people receiving ranitidine and nizatidine compared with people receiving other H2 blockers overall, by follow-up length, by cumulative dose, or by cancer site. These results may alleviate concerns of patients exposed to ranitidine/nizatidine, although further research with longer follow-up and including older people may be needed.

Declarations

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Conflicts of Interest/Competing Interests Masao Iwagami, Ryosuke Kumazawa, Yoshihisa Miyamoto, Yuri Ito, Miho Isihmaru, Kojiro Morita, Shota Hamada, Nanako Tamiya, and Hideo Yasunaga have no conflicts of interest that are directly relevant to the content of this article.

Availability of Data and Material The data were obtained from the Japan Medical Data Center (JMDC) Co., Ltd. (Tokyo, Japan). The JMDC data governance does not allow us to distribute patient data to other parties. Researchers may apply for data access at https://www.jmdc.co.jp/en/index. The codes used to define the exposure, outcome, and covariates for this study are provided in the Electronic Supplementary Material.

Ethics Approval This study was approved by the Institutional Review Board of The University of Tokyo.

Consent to Participate The need for informed consent was waived because of the anonymous nature of the data.

Consent for Publication Patient privacy and confidentiality were preserved because each individual's identifier was removed at the time of the database creation.

Code Availability STATA Version 16 (StataCorp, College Station, TX, USA) is commercially available. A custom code is available from the corresponding author on reasonable request.

Authors' Contributions Masao Iwagami planned the study, conducted the analysis, and wrote the first draft of the manuscript. Ryosuke Kumazawa, Yoshihisa Miyamoto, Miho Isihmaru, and Kojiro Morita extracted the data and assisted with the data analysis. Yuri Ito, Shota Hamada, and Nanako Tamiya assisted with the interpretation of the results and writing of the manuscript. Hideo Yasunaga supervised the study and assisted with the writing of the manuscript. All authors have read and approved the final manuscript.

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