UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION

MDL NO 2924
20-MD-2924

JUDGE ROBIN L ROSENBERG
MAGISTRATE JUDGE BRUCE REINHART

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THIS DOCUMENT RELATES TO: ALL CASES

MDL PLAINTIFFS' *EXPEDITED* MOTION TO SUBMIT SUPPLEMENTAL EXPERT REPORTS AND INCORPORATED MEMORANDUM OF LAW

MDL Plaintiffs request leave to submit supplemental reports for five of their general causation experts, Anne McTiernan, M.D., Ph.D., Patricia Moorman, M.S.P.H., Ph.D., Andrew Salmon, D.Phil., C.Chem., Paul Michaels, M.D., and Jennifer Le, Pharm.D., based on the September 30, 2022 publication of the long-awaited Wang Study that was discussed during the *Daubert* hearings held on September 21-22, 2022.

I. BASIS FOR EXPEDITED TREATMENT

Last Friday, September 30, 2022, the International Journal of Environmental Research and Public Health published the much-anticipated Wang Study entitled, *Pharmacoepidemiological Research on N-Nitrosodimethylamine-Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study.*[1] The Wang Study directly relates to several Ranitidine epidemiology issues discussed during the ongoing *Daubert* proceedings before this Court. Expedited treatment of this motion is necessary pursuant to S.D. Fla. L.R. 7.1(d)(2) because the continued *Daubert* hearing is scheduled for this Friday, October 7, 2022, and MDL Plaintiffs'

[1] Int. J. Environ. Res. Public Health 2022, 19, 12469, available at https://doi.org/10.3390/ijerph191912469 and attached as Exhibit A.

experts' supplemental reports, which are limited to addressing the recent Wang Study, are pertinent to the *Daubert* motions pending before this Court.

II. RELEVANT BACKGROUND

The long-anticipated Wang Study was published last Friday and directly addresses several key issues addressed in the pending *Daubert* motions. A pre-publication summary of the Study was presented at the American Gastroenterology Association's Digestive Disease Week Conference, and that presentation was cited in the briefing. *E.g.*, D.E. 5841 at 59. The Study answers "several questions using propensity score matching with a large population size selected from a high-quality nationwide and population-based database with a long follow-up period to assess the relationship between the cumulative individual cancer incidence and long-term ranitidine use." *See* Ex. A at 1.

The study is highly relevant for this Court to consider for many reasons, of which four stand out. First, it provides ranitidine-specific epidemiological evidence of increased risk for each designated cancer (including dose-response analyses for some cancers). Second, it includes sub-analyses using famotidine and PPIs as active comparators, a form of analysis Defendants have emphasized. Third, it discusses multiple other ranitidine-specific epidemiological studies, identifying particular limitations in those studies that are similar to the limitations MDL Plaintiffs' experts have identified (short follow-up, low exposure, young age, and so forth). Fourth, it analyzes scientific literature on NDMA, which Defendants claim no scientist outside this litigation has ever done.

Given the importance of the causal association between ranitidine use and cancers found by Wang, which has broad implications for the *Daubert* motions pending before the Court, five of MDL Plaintiffs' general causation experts have prepared short, targeted supplemental reports that

only address this Study prior to the close of the *Daubert* record. Thus, MDL Plaintiffs attach the following:

Exhibit B – Supplemental Report of Anne McTiernan, M.D., Ph.D.;

Exhibit C – Supplemental Report of Patricia Moorman, M.S.P.H., Ph.D.;

Exhibit D – Supplemental Report of Andrew Salmon, D.Phil., C.Chem.;

Exhibit E – Supplemental Report of Paul Michaels, M.D.; and

Exhibit F – Supplemental Report of Jennifer Le, Pharm.D.

III. ARGUMENT

Rule 26(e)(2) imposes a duty upon parties to supplement their expert reports which are authorized to be filed until "the time the party's pretrial disclosures under Rule 26(a)(3) are due." Fed. R. Civ. P. 26(e)(2). No trial date has been set in this MDL, and so no pretrial disclosure deadline has passed. Courts have held that parties should be permitted to timely supplement their expert reports with new scientific studies as they emerge. *See, e.g., In re Gadolinium-Based Contrast Agents Prod. Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 8334226, at *2 (N.D. Ohio Dec. 6, 2010), *aff'd sub nom. Decker v. GE Healthcare Inc*., 770 F.3d 378 (6th Cir. 2014). Indeed, the Brand Defendants themselves have acknowledged this is the proper course. The Brand Defendants previously recognized, in the context of the motion to modify PTO 30, that supplementation of expert reports is "typical" of MDL practice when new data emerges. *See* Exh. G, June 9, 2021 Hearing Transcript at 16:20-21 ("In cases like this, it is typical that, if something happens later on, somebody moves to supplement.").

Motions for leave to supplement expert reports regarding newly published studies appears to be the preferred method for introducing such evidence even after *Daubert* rulings have been issued. *See In re Johnson & Johnson Talcum Powder Prods. Marketing, Sales Practices and*

Prods. Litig., 509 F.Supp.3d 116, 129 n. 6 (D.N.J. 2020) (noting "that the parties may seek leave from the Court to supplement an expert's report based on any new and relevant studies," and that if such new evidence "impact[ed] my *Daubert* decisions made in this Opinion, I may amend my rulings at a later time."); *In re C.R. Bard, Inc*., 948 F. Supp. 2d 589, 650 (S.D.W. Va. 2013), on reconsideration in part (June 14, 2013) (noting "plaintiff could have, within the parameters of Rules 26 and 37, filed a supplemental expert report").

Even opinions striking untimely reports have recognized the propriety of supplementing an expert's report based on truly new information. *See Cook v. Royal Caribbean Cruises, Ltd.*, No. 11-20723-CIV, 2012 WL 2319089, at *2 (S.D. Fla. June 15, 2012) ("If Plaintiff's two experts had issued supplemental reports based on information that was unavailable to them by the time of the discovery cutoff, then Plaintiff would be in a different situation."); *Guevara v. NCL (Bahamas) Ltd.*, 920 F.3d 710, 718 (11th Cir. 2019) (affirming a district court's decision to allow opinions that "incorporated or relied upon" previously unavailable information, but to strike opinions that "made no reference to any of" the unavailable information). That result follows either from Rule 26(e)(2) or from Rule 37(c)(1), which precludes the use of evidence that was not timely disclosed "unless the failure was substantially justified or is harmless." Here, the study was not published, and its underlying analysis was available only as a poster, before Friday September 30, which shows substantial justification. MDL Plaintiffs had no control over the publication schedule and gained no litigation advantage from the late publication.

MDL Plaintiffs made their intention to supplement the expert reports if the Wang Study were published known to Defendants and this Court. during the *Daubert* hearing on September 21, 2022. During that hearing, MDL Plaintiffs advised the Court that the Wang Study could be published at any time: "it has not yet been published. If it were to be published, we might try very

quickly to move to supplement ….” Sept. 21, 2022 *Daubert* Hr’g Tr. at 280:24-281:1. That has now happened, and this Court should consider it as part of the *Daubert* record.

IV. CONCLUSION

Based on the foregoing, this Court should grant MDL Plaintiffs’ expedited motion and accept the supplemental expert reports based on the September 30, 2022 publication of the Wang Study.

V. LOCAL RULE 7.1 CERTIFICATE

In accordance with S.D. Fla. L.R. 7.1., counsel for MDL Plaintiffs certify that they conferred with counsel for Brand Defendants regarding the relief sought in this motion. On October 3, 2022, Tracy Finken, Plaintiffs’ Co-Lead Counsel, spoke with Mark Cheffo, Defendants’ Co-Lead Counsel, to apprise Mr. Cheffo of MDL Plaintiffs intention to file this expedited motion for leave to supplement the expert reports. Ms. Finken requested that Defendants agree not to oppose the requested relief. Mr. Cheffo stated that he could not provide Defendants’ position until they had an opportunity to review the supplemental reports. The supplemental reports were served on Defendants on Tuesday afternoon, October 4. Defendants have not yet advised MDL Plaintiffs of their position with respect to the requested relief.

DATED: October 4, 2022.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on October 4, 2022, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF and that the foregoing document is being served on all counsel of record or parties registered to receive CM/ECF Electronic Filings.

/s/ *Robert C. Gilbert*
Robert C. Gilbert

EXHIBIT A

International Journal of *Environmental Research and Public Health*

MDPI

Article

Pharmacoepidemiological Research on N-Nitrosodimethylamine-Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study

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Simple Summary: There is a lack of published data regarding the association between N-nitrosodimethylamine and human cancer risks. Hence, this study answers several questions using propensity score matching with a large population size selected from a high-quality nationwide and population-based database with a long follow-up period to assess the relationship between the cumulative individual cancer incidence and long-term ranitidine use.

Abstract: N-Nitrosodimethylamine (NDMA), a carcinogenic chemical, has recently been identified in ranitidine. We conducted a population-based study to explore ranitidine use and cancer emergence over time. Using the Taiwan National Health Insurance Research Database, a population-based cohort study was conducted. A total of 55,110 eligible patients who received ranitidine between January 2000 and December 2018 were enrolled in the treated cohort. We conducted a 1:1 propensity-score-matching procedure to match the ranitidine-treated group with the ranitidine-untreated group and famotidine controls for a longitudinal study. The association of ranitidine exposure with cancer outcomes was assessed. A multivariable Cox regression analysis that compared cancer risk with the untreated groups revealed that ranitidine increased the risk of liver (hazard ratio (HR): 1.22, 95% confidence interval (CI): 1.09–1.36, $p < 0.001$), lung (HR: 1.17, CI: 1.05–1.31, $p = 0.005$), gastric (HR: 1.26, CI: 1.05–1.52, $p = 0.012$), and pancreatic cancers (HR 1.35, CI: 1.03–1.77, $p = 0.030$). Our real-world observational study strongly supports the pathogenic role of NDMA contamination, given that long-term ranitidine use is associated with a higher likelihood of liver cancer development in ranitidine users compared with the control groups of non-ranitidine users treated with famotidine or proton-pump inhibitors.

Keywords: ranitidine; famotidine; cancers; N-nitrosodimethylamine (NDMA); propensity score matching (PSM)

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Citation: Wang, C.-H.; Chen, I.-I.; Chen, C.-H.; Tseng, Y.-T. Pharmacoepidemiological Research on N-Nitrosodimethylamine-Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study. *Int. J. Environ. Res. Public Health* **2022**, *19*, 12469. https://doi.org/10.3390/ijerph191912469

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1. Introduction

Ranitidine, a histamine-2 receptor antagonist, inhibits gastric acid secretion when treating gastroesophageal reflux disease and peptic ulcers [1]. Additionally, according to the data from the Food and Drug Administration (FDA) Adverse Event Reporting System, elevated and significant proportional reporting ratios (PRRs) were observed for pharyngeal, esophageal, stomach, colorectal, liver, and pancreatic cancers, including elevated PRRs for anal and gallbladder cancers [2].

In 2019, the U.S. FDA declared that N-nitrosodimethylamine (NDMA), with the formula (CH3)2NNO, identified in medicines containing valsartan and ranitidine, is a

member of N-nitrosamines and a known carcinogen, according to laboratory results [3–5]. The FDA's testing of ranitidine products revealed that NDMA levels were nine times greater than the FDA's recommended limit, resulting in global recalls [6,7]. Several studies have also reported that NDMA could be oncogenic in animals [8]. According to the International Agency for Research on Cancer report, NDMA has been proven to belong to group 2A and to be "probably carcinogenic to humans" [9].

A study also reported that high ranitidine doses combined with nitrite produced DNA fragmentation in rodents' livers and gastric mucosa [10]. Many observational human studies have reported that consuming a high number of NDMA-contaminated foods may be linked to an increased risk of stomach and colon cancers [11,12]. Additionally, detailed experimental animal studies showed that cancer risk may increase with NDMA exposure through inhalation or oral delivery and that tumors developed in the lungs, liver, kidneys, and bile ducts in animals [13]. Several studies previously examined the carcinogenic effects of NDMA on humans, although they were equivocal. Some authors reported no association between ranitidine use and cancer risk [14–16], whereas others supported the connection [17–20]. In addition to cancers caused by NDMA contamination, multiple studies reported that acid-suppressive agents, such as proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), were linked to gastric [21,22] and liver cancers [23–26]. However, these reports were contradictory, and the data were not sufficient to reach definite conclusions. The conflicting results of studies underlie the lack of concrete evidence supporting the role of ranitidine in cancer development. Therefore, we aimed to conduct a large-scale, long-term follow-up cohort study to investigate ranitidine use and the subsequent emergence of cancer over time in a real-life setting.

2. Materials and Methods

2.1. Data Source

This study used Taiwan's National Health Insurance Database (NHIRD), which is a population-based claims database, and a cross-sectional survey participated in by over 99% of Taiwan's population. We included all medical services, procedures, and prescription medication data from 1 January 2000 to 31 December 2018. The diagnoses recorded in the NHIRD are coded in accordance with the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), and Tenth Revision, Clinical Modification (ICD-10-CM).

Considering that the NHIRD dataset consists of encrypted secondary data, each person is impossible to identify; thus, the informed consent requirement was waived. The Research Ethics Committee of Show Chwan Memorial Hospital approved the study protocol on 14 December 2021 (IRB-No: 1101105).

2.2. Study Design and Study Participants

The total doses for each ranitidine prescription during the follow-up period were calculated to indicate the duration of ranitidine exposure. As the World Health Organization proposed, one defined daily dose (DDD) of ranitidine was 300 mg/day [27]. We defined 90 DDDs as the valid treatment for patients with reflux esophagitis and peptic ulcer disease treated with 300 mg ranitidine daily for 3 months [28,29]. Patients prescribed ranitidine at $\geq$90 DDDs were assigned to the ranitidine cohort, whereas those who never used ranitidine belonged to the non-ranitidine cohort.

We investigated whether a dose–response relationship exists between ranitidine and cancer diagnosis. For the sensitivity analysis, we grouped the patient follow-up period into four intervals according to the cumulative dose, starting from the first prescription: 90–180, 181–270, 271–360, and >360 DDDs.

2.3. Potential Confounders

The exclusion criteria were as follows: age < 40 years, diagnosis with cancer before the index date, ranitidine use <90 DDDs, and follow-up <1 year.

We enrolled ranitidine users who were matched for exact age, sex, the Charlson comorbidity index (CCI), comorbidities (hypertensive cardiovascular disease (HCD0, hyperlipidemia, diabetes mellitus (DM), and chronic kidney disease (CKD)), medications (aspirin, statins, angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, spironolactone, glucocorticoids, and selective serotonin reuptake inhibitors (SSRIs), and antiviral therapy for hepatitis B or C virus (HBV and HCV, respectively) infection), and the index date.

The final matched cohort consisted of 55,110 patients who were evaluated from the index date until the target cancer onset, death, or the end of the study period (31 December 2018).

2.4. Covariate Assessment

The main confounding factors were based on a recent study investigating the association between N-nitrosodimethylamine and cancer. We adjusted for the following covariates that potentially affect cancer incidence: age, sex, and medication history (low-dose aspirin, statins, ACEIs, β-blockers, spironolactone, glucocorticoids, SSRIs, and antiviral treatment for chronic hepatitis B or C).

We also considered the following comorbidities: HCD (ICD-9 codes 401–405; ICD-10 codes I10–I15), hyperlipidemia (ICD-9 code 272; ICD-10 code E78), DM (ICD-9 code 250; ICD-10 codes E10.0, E10.1, E10.9, E11.0, E11.1, and E11.9), CKD (ICD-9 code 585; ICD-10 code N18), and CCI.

2.5. Main Outcome Measurements

We assessed the following cancer categories for the first cancer diagnosis: liver cancer (ICD-9 code 155; ICD-10 code C22), oral cancer (ICD-9 codes 140–149; ICD-10 codes C00–C14), esophageal cancer (ICD-9 code 150; ICD-10 code C15), gastric cancer (ICD-9 code 151; ICD-10 code C16), colon cancer (ICD-9 code 153; ICD-10 code C18), rectal cancer (ICD-9 code 154; ICD-10 codes C19–C21), pancreatic cancer (ICD-9 code 157; ICD-10 code C25), lung cancer (ICD-9 code 162; ICD-10 codes C33 and C34), bone cancer (ICD-9 code 170; ICD-10 codes C40 and C41), bladder cancer (ICD-9 code 188; ICD-10 code C67), renal cancer (ICD-9 code 189; ICD-10 codes C65, C66, and C68), thyroid cancer (ICD-9 code 193; ICD-10 code C73), skin cancer (ICD-9 codes 172–173; ICD-10 code C44), breast cancer in females (ICD-9 code 174; ICD-10 code C50), uterine cancer (ICD-9 code 179; ICD-10 code C55), cervical cancer (ICD-9 code 180; ICD-10 code C53), ovarian cancer (ICD-9 code 183; ICD-10 codes C56 and C570–C574), prostate cancer (ICD-9 code 185; ICD-10 codes C61), and overall cancer. For breast, uterine, cervical, and ovarian cancers, the analysis was restricted to females, and prostate cancer was restricted to males.

2.6. Exposure Definition and Follow-Up

In this study, we adopted a new-user design with 1 year as the washout period to eliminate the influence of external factors in patients with newly diagnosed cancer [30]. Patients with no predefined outcomes or those who died during the follow-up were censored. We defined the index date for each ranitidine user as the date of their first prescription. For their corresponding matched comparison group, the index date was set to be that of their matched individual with ranitidine use. All patients were followed up from the index date to 2018. The mean follow-up period was 9.56 ± 5.96 (median: 8.42) years for the ranitidine cohort and 9.70 ± 5.96 (median: 8.58) years for the non-ranitidine cohort. All prescriptions, diagnostic outcomes, and deaths were ascertained until 31 December 2018. For all groups, the follow-up duration was defined as the interval from the date of enrollment to the date of cancer diagnosis, death, or the end of the follow-up period, whichever came first.

2.7. Statistical Analysis

Categorical variables were compared using the McNemar test. Continuous variables such as the prescription and medical records as baseline characteristics were compared using paired *t*-tests. To reduce potential selection bias, we used propensity score match-

ing (PSM) to balance the differences in proportions, such as comorbidities, between the ranitidine and non-ranitidine cohorts.

For a robust propensity score matching, 1:1 full matching without replacement was performed. Therefore, the regression model was specified correctly relative to the population regression function of the outcome variable on the treatment and all covariates used for matching. Therefore, trimming techniques were not employed in the weighting approach [31,32]. PSM was performed using multivariate logistic regression analysis and nearest-neighbor matching with the R package "MatchIt" (version 4.3.4).

We used Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer risk for ranitidine users in comparison with non-ranitidine users. To confirm the stability and robustness of our model, all hazard ratios and their 95% CIs were modified using the bootstrapping method [33,34]. The outcomes of the different study cohorts were estimated using the Kaplan–Meier method, and the differences in curves were examined using the log-rank test. Sensitivity analysis was conducted to validate the individual events from the index date to the end of the study in different DDD exposure groups using Cox proportional hazards regression models and the Kaplan–Meier method.

The competing risks of death were adjusted using the R package "cmprsk" (version 2.2–11), and the regression model was assessed according to Fine and Gray. All data management procedures were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and R version 3.4.3 (R Core Team, 2017). A p-value of <0.05 was considered statistically significant.

3. Results

In the NHIRD database, we found 290,990 ranitidine users and 1,709,128 non-ranitidine users within the study period (Figure 1). In accordance with the exclusion criteria, 75,715 and 1,022,217 patients were finally included in the ranitidine and non-ranitidine cohorts, respectively. Using PSM, we matched the ranitidine cohort (n = 55,110) with the non-ranitidine cohort (n = 55,110) in a 1:1 model. Figure 1 illustrates the flowchart of patient selection.

Patients from the non-ranitidine cohort who were statistically matched with those from the ranitidine cohort were selected in consideration of the following factors: age, sex, CCI, and comorbidities, including HCD, hyperlipidemia, DM, and CKD.

Certain medications (aspirin, statins, ACEIs, β-blockers, spironolactone, glucocorticoids, SSRIs, and antiviral therapy for HBV or HCV infection) and the index date (the exact date of diagnosis) were potential confounders for most cancers. Table 1 shows the baseline characteristics of the well-balanced, 1:1 matched cohort. Sex, age, CCI scores, and the follow-up period were fully matched between the ranitidine and non-ranitidine cohorts. Overall, the male–female ratio was 47.8:52.2 (p = 1.000), with mean values of 66.8 ± 14.1 (p = 1.000), 3.77 ± 2.78 (p = 1.000), and 9.2 ± 5.9 years (p = 1.000) for age, CCI, and follow-up duration, respectively. The median follow-up duration was 8.3 years.

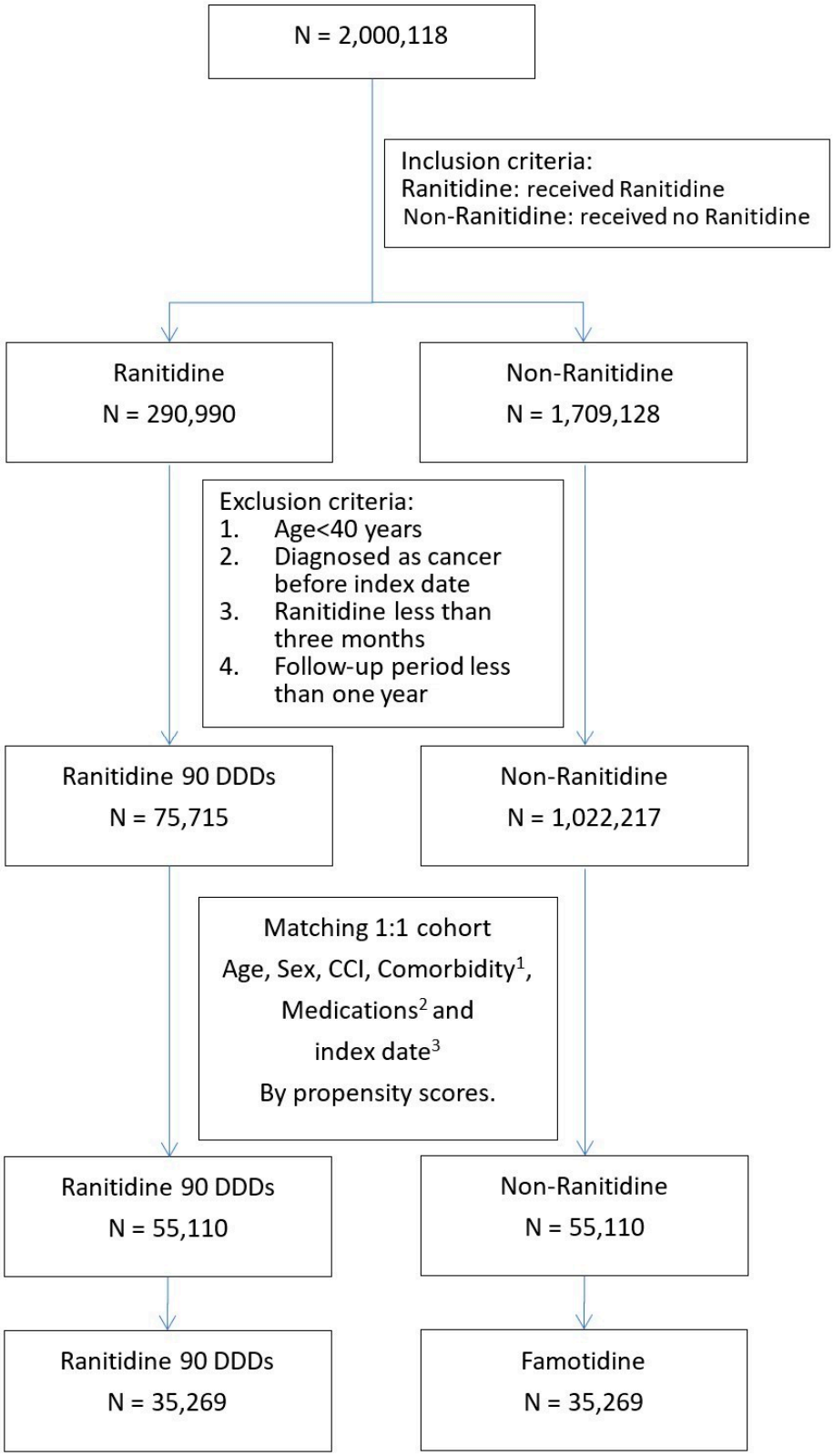


Figure 1. Flowchart of the selection of study patients. [1] Comorbidities: hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, and chronic kidney disease. [2] Medications: aspirin, statins, angiotensin-converting enzyme inhibitors, β-blockers, famotidine, spironolactone, glucocorticoids, selective serotonin reuptake inhibitors, and antiviral therapy for hepatitis B or C. [3] Index date: exact date of the first prescription.

Table 1. Baseline characteristics of the non-ranitidine cohort and ranitidine cohort with over 90 DDDs.

Characteristics		Untreated n = 55,110	%	Ranitidine n = 55,110	%	p-Value
Sex	Female	28,794	52.2%	28,794	52.2%	1.000
	male	26,316	47.8%	26,316	47.8%	
Age (mean ± SD)		66.8 ± 14.1		66.8 ± 14.1		1.000
CCI	0–1	12,444	22.6%	12,444	22.6%	1.000
	2–3	16,205	29.4%	16,205	29.4%	
	4–5	12,799	23.2%	12,799	23.2%	
	>5	13,662	24.8%	13,662	24.8%	
HCD	No	22,204	40.3%	22,204	40.3%	1.000
	Yes	32,906	59.7%	32,906	59.7%	
Hyperlipidemia	No	26,072	47.3%	26,072	47.3%	1.000
	Yes	29,038	52.7%	29,038	52.7%	
DM	No	37,598	68.2%	37,598	68.2%	1.000
	Yes	17,512	31.8%	17,512	31.8%	
CKD	No	49,704	90.2%	49,704	90.2%	1.000
	Yes	5406	9.8%	5406	9.8%	
Aspirin	No	25,810	46.8%	25,810	46.8%	1.000
	Yes	29,300	53.2%	29,300	53.2%	
Statins	No	32,089	58.2%	32,089	58.2%	1.000
	Yes	23,021	41.8%	23,021	41.8%	
ACEIs	No	31,214	56.6%	31,214	56.6%	1.000
	Yes	23,896	43.4%	23,896	43.4%	
β-Blockers	No	16,047	29.1%	16,047	29.1%	1.000
	Yes	39,063	70.9%	39,063	70.9%	
Famotidine	No	19,841	36.0%	19,841	36.0%	1.000
	Yes	35,269	64.0%	35,269	64.0%	
Spironolactone	No	48,320	87.7%	48,320	87.7%	1.000
	Yes	6790	12.3%	6790	12.3%	
Glucocorticoids	No	5748	10.4%	5748	10.4%	1.000
	Yes	49,362	89.6%	49,362	89.6%	
SSRIs	No	44,749	81.2%	44,749	81.2%	1.000
	Yes	10,361	18.8%	10,361	18.8%	
Antiviral therapy	No	54,271	98.5%	54,271	98.5%	1.000
	Yes	839	1.5%	839	1.5%	

Abbreviations: DDDs, defined daily doses; SD, standard deviation; CCI, Charlson comorbidity index; HCD, hypertensive cardiovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitor; SSRIs, selective serotonin reuptake inhibitors.

As shown in Figure 2, the ranitidine cohort showed a significantly higher prevalence of liver cancer (1.1% vs. 1.3%; p = 0.012), gastric cancer (0.4% vs. 0.5%; p = 0.037), and lung cancer (1.0% vs. 1.2%; p = 0.033) and a higher overall cancer rate (8.0% vs. 8.5%; p = 0.001) than the non-ranitidine cohort. In terms of the cumulative incidence rates and HRs, ranitidine use was associated with overall cancer (HR, 1.10; 95% CI, 1.06–1.15), liver cancer (HR, 1.22; 95% CI, 1.09–1.36), gastric cancer (HR, 1.26; 95% CI, 1.05–1.52), pancreatic cancer (HR, 1.35; 95% CI, 1.03–1.77), and lung cancer (HR, 1.17; 95% CI, 1.05–1.31) compared with non-ranitidine use. No significant associations were observed for the 14 other cancers. In the Kaplan–Meier analysis, the ranitidine cohort exhibited a significantly higher risk of developing liver cancer (log-rank test, p = 0.005), lung cancer (p = 0.016), gastric cancer (p = 0.025), and pancreatic cancer (p = 0.043) than the non-ranitidine cohort (Figure 3).

Cancers	untreated	%	ranitidine	%	*p*-value	HR (95% CI)	*p*-value
All cancers	4399	8.00%	4682	8.50%	0.001	1.10(1.06–1.15)	<0.001
Prostate cancer	306	1.20%	313	1.20%	0.404	1.07(0.91–1.25)	0.411
Ovarian cancer	54	0.20%	42	0.10%	0.131	0.79(0.53–1.18)	0.249
Cervix cancer	166	0.60%	155	0.50%	0.288	0.95(0.76–1.18)	0.635
Uterine cancer	67	0.20%	53	0.20%	0.117	0.80(0.55–1.14)	0.213
Breast cancer (female)	407	1.40%	455	1.60%	0.053	1.13(0.99–1.29)	0.078
Skin cancer	203	0.40%	189	0.30%	0.479	0.97(0.79–1.18)	0.748
Thyroid cancer	96	0.20%	90	0.20%	0.661	0.94(0.71–1.26)	0.698
Renal cancer	154	0.30%	181	0.30%	0.14	1.21(0.98–1.50)	0.080
Bladder cancer	177	0.30%	181	0.30%	0.437	1.06(0.86–1.30)	0.592
Bone cancer	3	0.00%	4	0.00%	0.5	1.35(0.30–6.02)	0.696
Lung cancer	575	1.00%	649	1.20%	0.033	1.17(1.05–1.31)	0.005
Pancreas cancer	93	0.20%	121	0.20%	0.056	1.35(1.03–1.77)	0.030
Rectal cancer	286	0.50%	304	0.60%	0.483	1.10(0.93–1.29)	0.266
Colon cancer	527	1.00%	492	0.90%	0.271	0.96(0.85–1.09)	0.569
Gastric cancer	210	0.40%	255	0.50%	0.037	1.26(1.05–1.52)	0.012
Esophageal cancer	82	0.10%	101	0.20%	0.161	1.27(0.95–1.70)	0.107
Oral Cancer	191	0.30%	161	0.30%	0.122	0.86(0.70–1.06)	0.153
Liver cancer	619	1.10%	711	1.30%	0.012	1.22(1.09–1.36)	<0.001

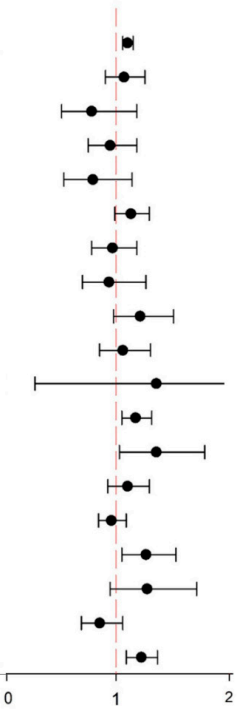


Figure 2. Number and proportion of 18 different cancer reports in the ranitidine and non-ranitidine cohorts and the associated proportional reporting ratios and 95% confidence intervals in multivariate Cox proportional hazards regression adjusted for competing mortality.

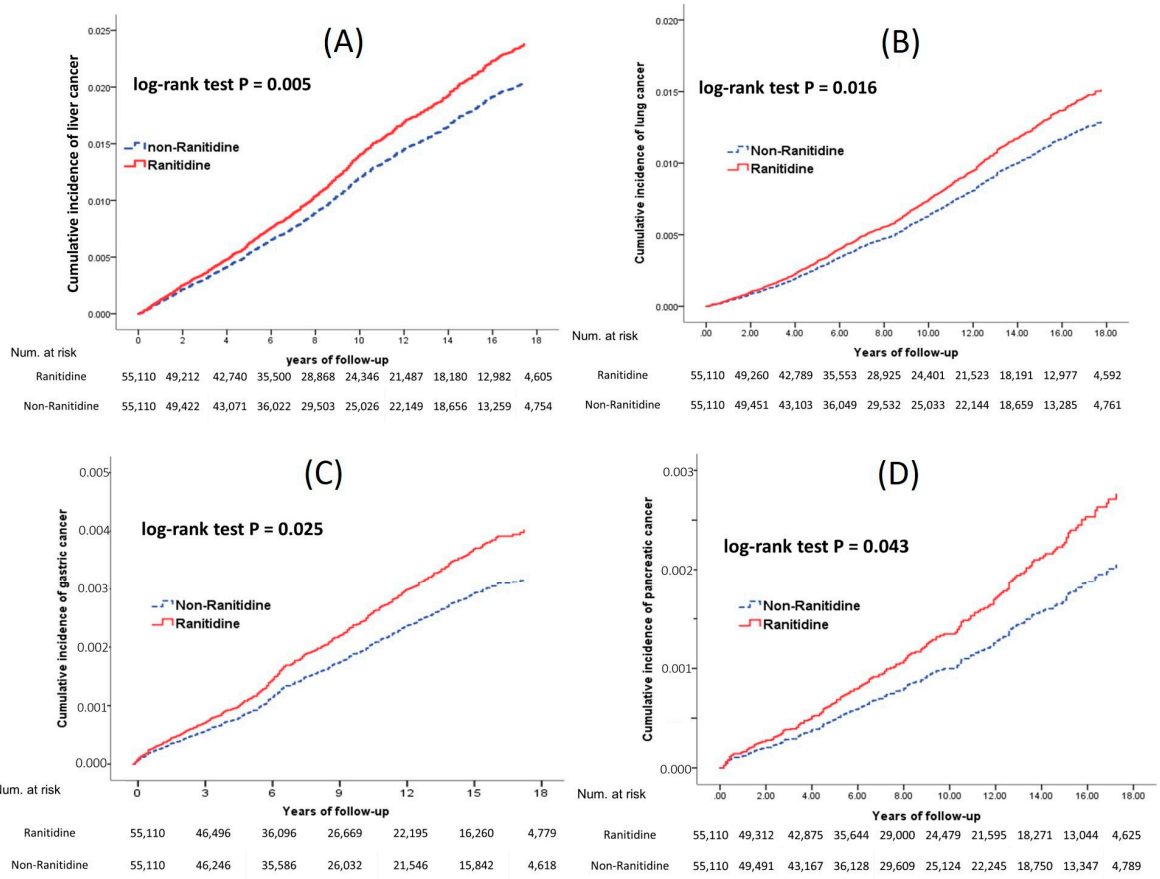


Figure 3. Cumulative incidences of single cancers after adjustment for competing risks. (**A**) Liver cancer, (**B**) lung cancer, (**C**) gastric cancer, and (**D**) pancreatic cancer.

Table 2 shows the incidence of each cancer. The incidence rate was 9.19 per 1000 person-years in the ranitidine group and 8.49 per 1000 person-years in the non-ranitidine group. The incidence rates of certain cancers were greater in the group exposed to ranitidine than in the unexposed group. Ranitidine use was associated with some individual cancers with a high incidence rate (per 1000 person-years); these cancers were liver (1.35 vs. 1.16), lung (1.23 vs. 1.07), gastric (0.48 vs. 0.39), and pancreatic (0.23 vs. 0.17) cancers.

Table 2. Incidence rates of individual cancers (per 1000 person-years).

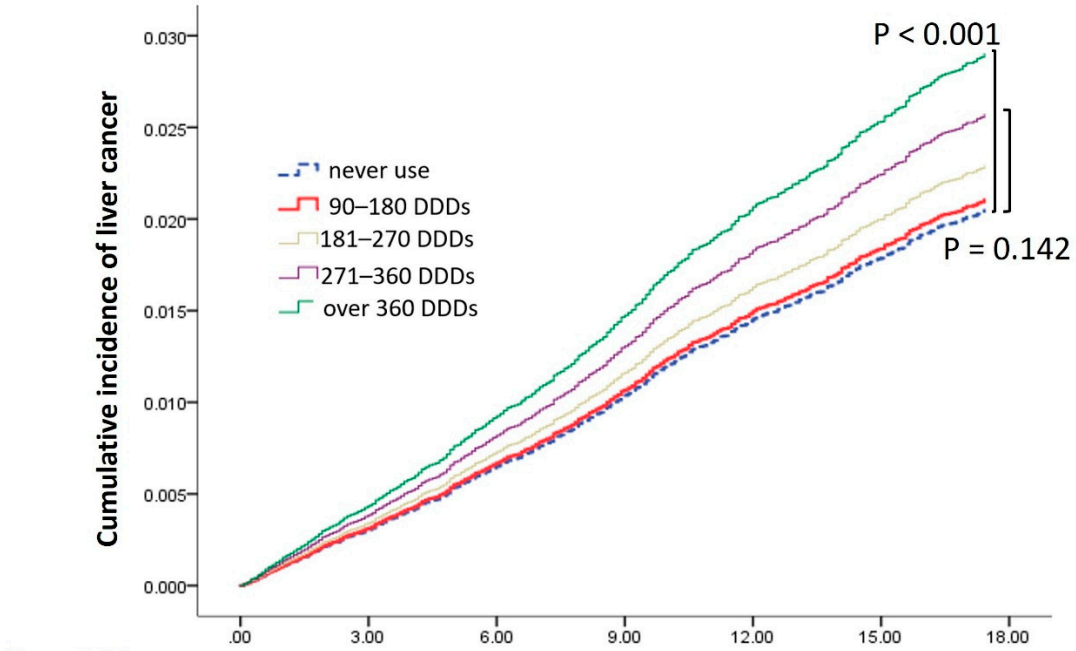
Cancers	Untreated	Incidence Rate *	(95% CI)	Ranitidine	Incidence Rate *	(95% CI)
Liver cancer	619	1.16	(1.07–1.25)	711	1.35	(1.25–1.45)
Oral Cancer	191	0.36	(0.30–0.41)	161	0.30	(0.26–0.36)
Esophageal cancer	82	0.15	(0.12–0.19)	101	0.19	(0.16–0.23)
Gastric cancer	210	0.39	(0.34–0.44)	255	0.48	(0.43–0.55)
Colon cancer	527	0.99	(0.90–1.07)	492	0.93	(0.85–1.02)
Rectal cancer	286	0.53	(0.47–0.60)	304	0.58	(0.51–0.64)
Pancreas cancer	93	0.17	(0.14–0.21)	121	0.23	(0.19–0.27)
Lung cancer	575	1.07	(0.98–1.16)	649	1.23	(1.14–1.33)
Bone cancer	3	0.01	(0.00–0.02)	4	0.01	(0.00–0.02)
Bladder cancer	177	0.33	(0.28–0.38)	181	0.34	(0.30–0.40)
Renal cancer	154	0.29	(0.25–0.33)	181	0.34	(0.30–0.40)
Thyroid cancer	96	0.18	(0.14–0.21)	90	0.17	(0.14–0.21)
Skin cancer	203	0.38	(0.33–0.43)	189	0.36	(0.31–0.41)
Breast cancer (female)	407	0.76	(0.69–0.83)	455	0.86	(0.79–0.95)
Uterine cancer	67	0.12	(0.09–0.15)	53	0.10	(0.08–0.13)
Cervix cancer	166	0.31	(0.27–0.36)	155	0.29	(0.25–0.34)
Ovarian cancer	54	0.10	(0.08–0.13)	42	0.08	(0.06–0.11)
Prostate cancer	306	0.57	(0.51–0.63)	313	0.59	(0.53–0.66)
All cancers	4399	8.49	(8.24–8.73)	4682	9.19	(8.93–9.45)

* Incidence rate (per 1000 person-years).

3.1. Ranitidine Duration Effect on Cancer Development

The effect of ranitidine use on the risk of progression to significant individual cancers (e.g., liver cancer, gastric cancer, lung cancer, and pancreatic cancer) was assessed by multivariate Cox regression analysis adjusted for age, sex, CCI, co-medications (aspirin, statins, ACEIs, β-blockers, spironolactone, glucocorticoids, SSRIs, and antiviral therapy for HBV or HCV infection), comorbidities (HCD, hyperlipidemia, DM, and CKD), and the calendar date at the start of follow-up.

Ranitidine users were divided into groups according to drug exposure: 90–180 DDDs, 181–270 DDDs, 271–360 DDDs, >360 DDDs, and an unexposed group. After adjusting for potential confounders, we found that ranitidine use was a potential risk factor for liver cancer development. For patients with relatively limited exposure to ranitidine (<360 DDDs), ranitidine did not significantly affect the risk of developing liver cancer compared with nonusers (Figure 4). However, increased ranitidine exposure was associated with liver cancer risk. For patients with >360 DDDs, the adjusted HR of liver cancer development was 1.42 (95% CI: 1.22–1.66; $p < 0.001$) compared with that in the non-ranitidine group (Table 3).



Num. at risk

over 360 DDDs	14,787	12,546	9,009	5,733	4,611	3,349	1,098
271–360 DDDs	5,289	4,334	3,316	2,412	1,973	1,472	471
181–270 DDDs	10,844	9,202	7,354	5,668	4,741	3,531	985
90–180 DDDs	24,190	20,098	15,821	12,151	10,162	7,449	2,051
never use	55,110	46,420	36,022	26,605	22,149	16,208	4,754

Figure 4. Cumulative incidences of liver cancer for different prescription durations after adjustment for competing risks. Abbreviations: DDDs, defined daily doses.

Table 3. Estimates for the association between ranitidine use duration and cancer risk compared with non-ranitidine use by multivariate Cox proportional hazards regression.

	Liver Cancer	*p*	Gastric Cancer	*p*	Lung Cancer	*p*	Pancreatic Cancer	*p*
Never used	1.00		1.00		1.00		1.00	
90–180 DDDs *	1.03 (0.89–1.18)	0.690	1.26 (1.00–1.59)	0.049	1.25 (1.09–1.44)	0.002	1.64 (1.19–2.26)	0.003
181–270 DDDs	1.12 (0.93–1.34)	0.220	1.13 (0.82–1.54)	0.452	1.09 (0.90–1.32)	0.403	1.10 (0.69–1.77)	0.682
271–360 DDDs	1.26 (0.99–1.61)	0.064	1.27 (0.84–1.93)	0.252	1.31 (1.02–1.68)	0.032	0.92 (0.45–1.89)	0.816
Over 360 DDDs	1.42 (1.22–1.66)	<0.001	1.33 (1.02–1.74)	0.037	1.04 (0.87–1.24)	0.658	1.22 (0.80–1.85)	0.358

* Abbreviations: DDDs, defined daily doses.

Regression was adjusted for age, sex, the Charlson comorbidity index, co-medications (aspirin, statins, angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, glucocorticoids, selective serotonin reuptake inhibitors, and antiviral therapy for hepatitis B or C), comorbidities (hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, and chronic kidney disease), and calendar year at the start of follow-up.

3.2. Comparison between Ranitidine and Famotidine for the Association with Patient Outcomes

To avoid potential indication bias, we selected non-ranitidine users (control subjects) by PSM for the famotidine cohort, with a ranitidine–famotidine ratio of 1:1. This subgroup was added to determine whether the use of ranitidine increases the risk of developing cancers due to the related indication.

We screened the risk for cancer in the ranitidine (n = 35,269) and famotidine (n = 35,269) cohorts (Figure 1). Ranitidine users who were statistically matched with famotidine users were selected, adjusting for the following factors: age, sex, indications, co-medications, and comorbidities.

The prevalence of overall cancer was 3052 (8.7%) in the ranitidine group and 2924 (8.3%) in the famotidine group. The overall cancer risk was statistically different between these two groups (adjusted HR, 1.07; 95% CI, 1.02–1.12, $p = 0.010$). Significant differences were also observed in liver (adjusted HR, 1.22; 95% CI, 1.06–1.40, $p = 0.005$) and renal cancer (adjusted HR, 1.33; 95% CI, 1.02–1.73, $p = 0.034$) outcomes between the two groups (Table 4).

In the Kaplan–Meier analysis, we found that liver cancer risk was significantly different between the ranitidine and famotidine cohorts with a balanced model ($p = 0.019$, Figure 5A). Moreover, the liver cancer risk was significantly higher in the ranitidine cohort than in non-ranitidine with famotidine and non-ranitidine without famotidine cohorts ($p < 0.001$ and $p = 0.02$, respectively; Figure 5B). Therefore, the pattern of the cumulative incidence of liver cancer was the same in the non-ranitidine groups, regardless of famotidine use.

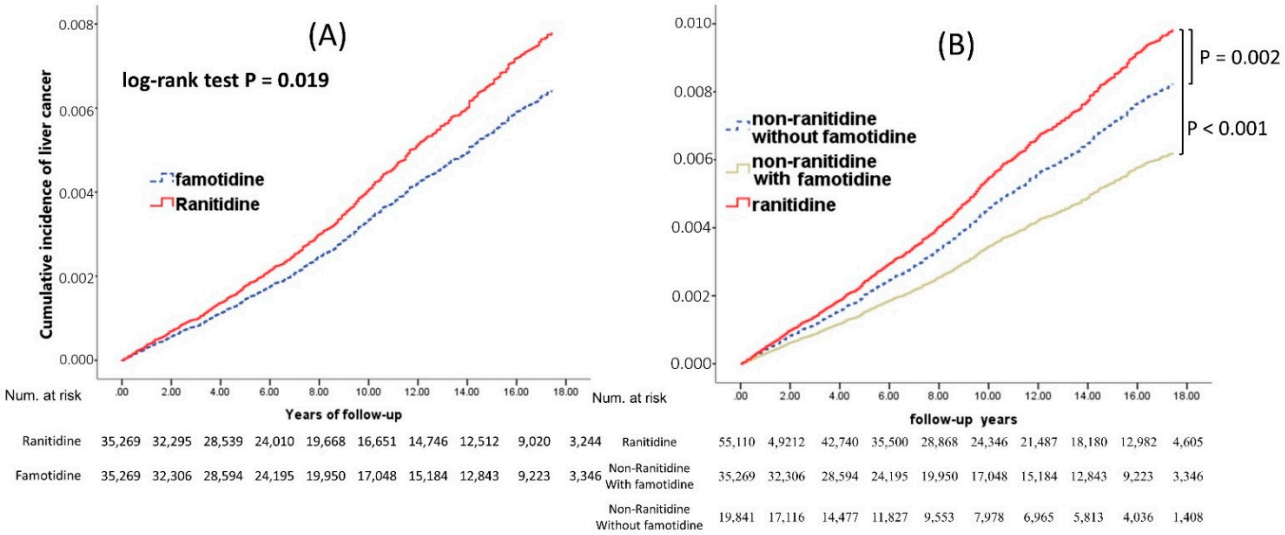


Figure 5. (**A**) Cumulative incidences of liver cancer between ranitidine and famotidine users after adjustment for competing risks. (**B**) Cumulative incidences of liver cancer among ranitidine, non-ranitidine with famotidine, and non-ranitidine without famotidine users after adjustment for competing risks.

Table 4. Risk of cancer between famotidine and ranitidine users.

Cancers	Famotidine	%	Ranitidine	%	Total	*p*-Value	HR (95% CI)	*p*-Value
Liver cancer	380	1.1%	442	1.3%	822	0.032	1.22(1.06–1.40)	0.005
Oral cancer	125	0.4%	107	0.3%	232	0.237	0.87(0.67–1.12)	0.286
Esophageal cancer	52	0.1%	60	0.2%	112	0.451	1.19(0.82–1.72)	0.364
Gastric cancer	142	0.4%	165	0.5%	307	0.208	1.19(0.95–1.49)	0.122
Colon cancer	365	1.0%	309	0.9%	674	0.033	0.86(0.74–1.01)	0.059
Rectal cancer	193	0.5%	195	0.6%	388	0.919	1.03(0.84–1.26)	0.768
Pancreas cancer	66	0.2%	80	0.2%	146	0.281	1.25(0.90–1.73)	0.186
Lung cancer	356	1.0%	400	1.1%	756	0.116	1.15(1.00–1.33)	0.052
Bone cancer *	n/a	n/a	n/a	n/a	n/a	n/a	1.51(0.25–9.03)	0.652
Bladder cancer	116	0.3%	117	0.3%	233	0.948	1.03(0.80–1.33)	0.830
Renal cancer	98	0.3%	128	0.4%	226	0.053	1.33(1.02–1.73)	0.034
Thyroid cancer	71	0.2%	63	0.2%	134	0.545	0.89(0.64–1.25)	0.514
Skin cancer	137	0.4%	137	0.4%	274	1.000	1.02(0.81–1.30)	0.842
All cancers	2924	8.3%	3052	8.7%	5976	0.086	1.07(1.02–1.12)	0.010

* According to the data protection policy of NHIRD, the data on cancers with <3 cases cannot be provided.

3.3. Comparison between Ranitidine and PPIs for Their Association with Liver Cancer

Considering another potential indication bias, we categorized the non-ranitidine users (control subjects) into those with and without PPI use. This subgroup analysis aimed to

determine whether ranitidine use increased liver cancer risk due to an alternative medicine with a related indication.

We screened the risk for cancer in the ranitidine (n = 55,110), ranitidine without PPI (n = 51,361), and ranitidine with PPI (n = 3749) cohorts (Figure 6). Ranitidine users were selected to adjust for the following factors: age, sex, indications, co-medications, and comorbidities.

The liver cancer risk was significantly higher in the ranitidine group than in the non-ranitidine without PPI group (adjusted HR, 1.16; 95% CI, 1.04–1.30, p = 0.006). Furthermore, liver cancer risk was significantly lower in the non-ranitidine with PPI group than in the non-ranitidine without PPI group (adjusted HR, 0.49; 95% CI, 0.33–0.75, p = 0.001). In the Kaplan–Meier analysis, we found that liver cancer risk was significantly higher in the ranitidine group than in the non-ranitidine without PPI and non-ranitidine with PPI groups (p = 0.032 and p < 0.001, respectively; Figure 6).

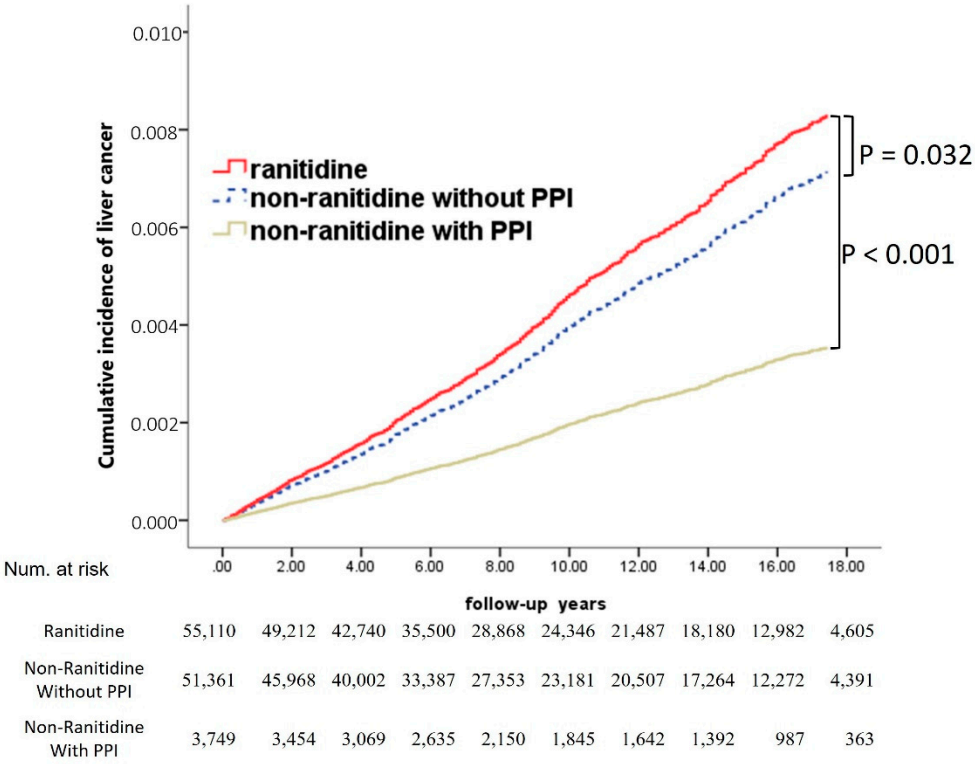


Figure 6. Cumulative incidences of liver cancer among ranitidine, non-ranitidine with PPI, and non-ranitidine without PPI users after adjustment for competing risks.

4. Discussion

The current research, a population-level epidemiologic study, evaluated cancer risk attributed to long-term ranitidine use with NDMA exposure, which was linked to a higher liver cancer risk than the non-ranitidine group and the famotidine group. Several epidemiological analyses have reported the public health concern of NDMA exposure, which has been linked to an increased risk of stomach and colon cancers [11,12,35]. The carcinogenic effects of NDMA theoretically result from inducing DNA-damaging metabolites in the gastrointestinal tract and liver, as suggested by animal studies. Notably, NDMA is metabolized in the liver by CYP2E1 to methyl diazonium, leading to mutations caused by methylation and the development of liver cancer [3,36]. Several studies have reported that hypoacidity due to acid-suppressive medication use also plays a critical role in the development of liver and gastric cancers. The hypothesized mechanisms include bacterial overgrowth, the formation of N-nitroso compounds, lipopolysaccharides, and deoxycholic acid, which have been linked to the development of liver cancer [37–43]. Additionally, higher gastrin levels following PPI or H2RA use may be associated with gastrointestinal malignancies [44,45].

Therefore, it is reasonable to assume that a link between acid-suppressive medication use and cancer development may be based on differing mechanisms. However, the clear data from our real-world observational study strongly support the pathogenic role of NDMA contamination, given that long-term ranitidine use is associated with a higher likelihood of cancer development in ranitidine users compared to the control groups of non-ranitidine users who were treated with PPIs or famotidine. Conversely, an increasing number of recent clinical and epidemiological studies [14,15] concluded that there is no convincing evidence of the carcinogenic potency of ranitidine. Nevertheless, the limitations of the two studies mentioned above should be considered since their small sample size and short follow-up duration may cause statistical bias and inaccurate conclusions. One notable strength of our study is the huge population size selected from a high-quality nationwide and population-based database with a long follow-up period of 18 years. Specifically, it was based on a cohort design of a seemingly prospective technique to explore ranitidine exposure and cancer outcomes. Additionally, outcome data were retrieved from formal cancer registries, which are more accurate than other sources. Using PSM, our study constructed an artificial control group (non-ranitidine users) with similar characteristics by combining it with additional matching for multiple prognostic factors or regression adjustment. Using these matches, we estimated the impact of ranitidine intervention on cancer risk, which showed increased odds of developing liver, lung, pancreatic, and gastric cancers. The Kaplan–Meier analysis of our 18-year dataset confirmed these findings.

We included a second active comparator group of individuals who were also prescribed famotidine, containing no NDMA and used for an almost identical indication, which might minimize potential bias to clarify potential confounding by indication.

The overall cancer risk was statistically different between these two groups compared with famotidine or non-ranitidine users. Notably, liver and renal cancers were more common among ranitidine users. Furthermore, the Kaplan–Meier analysis revealed that liver cancer risk was significantly higher in the ranitidine cohort than in the famotidine cohort. Our study observed this outcome using non-ranitidine users as a control group. Additionally, this result contradicts other reports [14,15]. Therefore, based on a direct comparison with either the non-ranitidine group or the famotidine group (similar indication to ranitidine users), only liver cancer displayed a significant association with long-term ranitidine use. This approach was used to ameliorate the implicit indication bias that occurs when the cancer risk is related to the indication for medication use but not to the use of the medication itself [46].

Another comparative approach in our study revealed the association of ranitidine usage with four individual cancers with a high incidence rate (per 1000 person-years), including liver, lung, gastric, and pancreatic cancers, compared with the general population. However, as stated by Roberts et al. [27,47,48], the preference for a pharmacoepidemiological study of drug safety is to develop a new-user design rather than a prevalent-user design in which patients have already been receiving therapy for some time before the study follow-up begins. Therefore, our study used 1 year as the washout period, during which the participants were taken off ranitidine, to remove the effects of treatment before the study initiation. Nonetheless, ranitidine still showed similar results after excluding "protopathic bias" [49], meaning that ranitidine use sometimes precedes cancer development before it is diagnosed.

A positive quality of our study is the use of PSM [50] in a population-based cohort design, which imitates a randomized trial to control for confounding factors that mostly depend on selecting the documented confounders used in the matching model [51]. These potential confounders in our study, which were causally associated with cancer development, include age, sex, CCI, comorbidities, and medications. Nonetheless, PSM cannot specifically balance unknown factors as randomized controlled trials (RCTs) do. Therefore, some experts [52] argued that substantial bias exists in a PSM study, which is one of our study limitations. However, despite having this limitation, PSM potentially takes advantage of the ability to generate a huge sample size from a large database within a short time.

Moreover, it is impractical and unethical to conduct an RCT to test the carcinogenicity of ranitidine in a patient.

In an additional dose–response subanalysis, given that drug–cancer associations are mostly dose-dependent, we further stratified the extent of NDMA exposure by cumulative ranitidine usage based on drug exposure: 90–180 DDDs, 181–270 DDDs, 271–360 DDDs, >360 DDDs, and an unexposed group. Notably, when considering the dose–response of ranitidine usage, there were significant trends of increased liver cancer risk with an increasing dose of ranitidine. However, there was no continuous dose–response relationship among the other individual cancers. Additionally, Iwagami et al. [14] reported contrary results, although they acknowledged a weakness in the study design due to the limited sample size and statistical power.

The conclusive results of our study after gathering data emphasize that consuming high levels of NDMA due to ranitidine use is linked to liver cancer development. Many current pieces of evidence based on several animal studies propose that NDMA affects liver cancer development, mostly originating from a detailed exploration of the molecular basis of NDMA's carcinogenic action [53–57]. For example, Souliotis et al. [58] reported that rats exposed to hepatocarcinogenic NDMA (0.2–2.64 ppm in the drinking water) for up to 180 days had a rapid accumulation of N7- and O6-methylguanine in the liver and white blood cells. The analysis of DNA, with the maximum adduct levels reached within 1–7 days dose-dependently, indicates that the accumulation of DNA damage and alterations in hepatocyte DNA replication during chronic NDMA exposure may influence the dose dependence of its carcinogenic efficacy. Notably, in the actual scenario, our result agrees with the above experimental data on the cumulative dose of ranitidine usage, which plays a vital role in hepatocarcinogenesis.

The present study has several limitations. First, it was constrained by the study design since we could not accurately estimate the NDMA level. Second, there were no data available in our database regarding certain confounders, such as alcohol consumption and cigarette smoking. Third, the patients' medication compliance cannot be detected from the NHIRD. Fourth, there was scarce information regarding over-the-counter ranitidine usage, which caused the underestimation of ranitidine exposure. Fifth, the NHIRD data used in our study was not the most recent. Sixth, the NHIRD lacks specific laboratory information. Finally, potential misdiagnosis, including comorbidities and cancer categories, is possible in the NHIRD due to the potential misclassification of ICD-9-CM and ICD-10-CM codes.

5. Conclusions

To conclude, the clinically meaningful results of this large-scale, longitudinal population-based cohort study using an excellent prescription and cancer database provide concrete evidence with very convincing long-term follow-up information for exploring the causative role of ranitidine in increasing the risk of carcinogenic effects on the liver, which was primarily caused by increasingly heavier ranitidine usage. However, to elucidate the underlying mechanisms of its causal association, further studies are necessary.

Author Contributions: Conceptualization, C.-H.W. and I.-I.C.; methodology, Y.-T.T.; software, Y.-T.T.; validation, Y.-T.T.; formal analysis, Y.-T.T.; investigation, C.-H.W. and I.-I.C.; resources, C.-H.W. and C.-H.C.; data curation, C.-H.W.; writing—original draft preparation, C.-H.W.; writing—review and editing, I.-I.C.; visualization, Y.-T.T.; supervision, C.-H.W.; project administration, C.-H.W.; funding acquisition, C.-H.W. and C.-H.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Show Chwan Memorial Hospital (IRB-No: 1101105) for studies involving humans.

Informed Consent Statement: Considering that the NHIRD dataset consists of encrypted secondary data, each person is impossible to identify; thus, the informed consent requirement was waived.

Data Availability Statement: The NHIRD protects personal electronic data by rigorous confidentiality guidelines. The results presented in the study are available from the NHIRD of Taiwan for researchers who meet the criteria for access to confidential data, which cannot be shared publicly because of legal restrictions imposed by the government of Taiwan under the "Personal Information Protection Act". Requests for data can be sent as a formal proposal to the NHIRD (https://dep.mohw.gov.tw/dos/np-2497-113.html, accessed on 1 August 2022). The contact information for needed data is: 886-2-85906828; Email: sthuiying@mohw.gov.tw.

Conflicts of Interest: The authors declare no conflict of interest. The funding sources had no role in the design, analysis, interpretation, or reporting of results or in the decision to submit the manuscript for publication.

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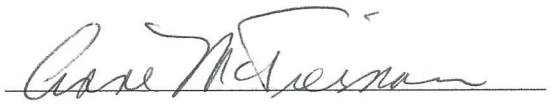
EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION *THIS DOCUMENT RELATES TO ALL CASES*	MDL NO. 2924 20-MD-2924

SUPPLEMENT TO EXPERT REPORT
ANNE MCTIERNAN, MD, PHD

Date: October 3, 2022



Anne McTiernan, MD, PhD

Addendum to Expert Report

Ranitidine and Cancer Risk in Humans

Re: Wang C-H, Chen I-I, Chen C-H, Tseng Y-T. Pharmacoepidemiological Research on N-Nitrosodimethylamine-Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study. *International Journal of Environmental Research and Public Health*. 2022; 19(19):12469. https://doi.org/10.3390/ijerph191912469

10/3/2022

Anne McTiernan, MD, PhD

Add to McTiernan expert report section "Epidemiologic Studies of Ranitidine and Risk of Multiple Cancers"

Taiwan National Health Insurance Research Database

On September 30, 2022, a study was published on the association between use of ranitidine and risk for several cancers. (Wang et al. 2022) (See Table 1 below for comparisons to the other ranitidine-cancer epidemiology studies in my expert report). The study used data from the Taiwan National Health Insurance Research Database, and conducted a population based cohort study. The Taiwan National Health Insurance Research Database, which is a claims database, as well as a survey in which 99% of the Taiwanese population provided information. Eligible patients for the ranitidine users group had used 90 or more defined daily doses (DDD) of ranitidine. Patients who had never used ranitidine were the comparison group. Separate comparison groups of famotidine users and proton pump inhibitor users were also formed, for secondary analyses. The study also investigated the association of total dose received to cancer risk (dose-response association). Other exclusion criteria were: aged less than 40 years, diagnosis with cancer before the index date, and follow-up for less than year.

The study matched ranitidine users to non-users on the following variables: age, sex, Charlson comorbidity index (a standard index of number of diseases patients have that predict mortality)(Charlson et al. 1987), hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus,

chronic kidney disease, specific medications (aspirin, statins, angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, glucocorticoids, selective serotonin reuptake inhibitors), and antiviral therapy for hepatitis B or C virus infection). The study defined the index date for each ranitidine user as the date of their first ranitidine prescription in the database. For each non-ranitidine-user, the index date was set to be that of their matched ranitidine user. The final matched cohort consisted of 55,110 ranitidine-using patients and 55,110 non-ranitidine-using patients who were evaluated from the index date until the target cancer onset, death, or the end of the study period (December 31, 2018). Cancers were determined by retrieval from formal cancer registries; cancers had ICD-9 or ICD-10 codes in the claims database.

Prescriptions, cancer outcomes, and deaths were ascertained from 2000 through 2018. For all groups, the follow-up duration was defined as the interval from the index date to the date of cancer diagnosis, death, or the end of the follow-up period, whichever came first. A total of 55,110 ranitidine users and 55,110 matched non-ranitidine users were included in the cohort. The mean follow-up period was 9.56 years (median 8.42 years, range 1 -18 years) for the ranitidine cohort and 9.70 years (median 8.58 years, range 1-18 years) for the non-ranitidine cohort.

The investigators handled potential for prevalent user bias by using a new-user design with a 1-year washout period to "eliminate the influence of external factors in patients with newly diagnosed cancer." The investigators selected a subgroup of nonusers who had used famotidine, and calculated relative risks for ranitidine versus famotidine users, as a method "to avoid potential indication bias," and selected famotidine users who were matched with ranitidine users. As a second such analysis, the investigators categorized the non-ranitidine-users into those who had used proton pump inhibitors versus those who had not.

Almost half of the cohort patients were followed for more than 9 years. During the follow-up, a total number of 4782 ranitidine users and 4399 non-ranitidine users developed any form of cancer. For individual cancers of interest to this litigation, the numbers of the 5 specific cancers were: liver (771 ranitidine, 619 nonusers); esophageal (101 ranitidine, 82 nonusers); stomach (255 ranitidine, 210 nonusers); pancreas (121 ranitidine, 93 nonusers); bladder (181 ranitidine, 177 nonusers).

The relative risks (hazard ratios) for these 5 cancers in ranitidine users compared with nonusers were: liver (1.22, 95% CI 1.09-1.36); esophageal (1.27, 95% CI 0.95-1.7); stomach (1.26, 95% CI 1.05-1.52); pancreas (1.35, 95% CI 1.03-1.77); bladder (1.06, 95% CI 0.86-1.3). All relative risks were above 1.0, and all but bladder and esophagus had confidence intervals that did not include 1.0. (The inclusion of 1.0 is likely to be related to low numbers of cases, especially for esophageal cancer.)

The authors present hazard graphs for liver, stomach, pancreas and lung cancers, which all show increasing risk with increasing years of follow-up (all $p < 0.05$) (see Figure 3 depicting the three cancers for this litigation—liver, stomach (gastric), and pancreas—at the end of this addendum). This pattern of increasing risk over time underscores the need to account for cancer latency times when conducting studies of carcinogenic effects of medications in humans. The patterns shown in the graphs are supportive of carcinogen effects in humans, where a carcinogen may not show much effect in early years of follow-up, but later show strong effects. Since there is likely variability in how long a latency period is needed in individuals and specific cancers, some patients will develop cancers earlier after exposure than other patients.

The dose-response analysis showed clear evidence of increasing liver cancer risks with increase total dose (daily defined dose, DDD) with relative risks for 90-180 DDD, 181-270 DDD, 271-360 DDD, and over 360 DDD of 1.03, 1.12, 1.26, and 1.42, respectively (see Figure 4 at end of this addendum). For stomach cancer, there was a trend toward increasing risk with increasing dose, with relative risks for 90-180 DDD, 181-270 DDD, 271-360 DDD, and over 360 DDD of 1.26, 1.13, 1.27, and 1.33, respectively. Clear dose-response relationships were not seen for pancreas cancer. Neither esophageal nor bladder cancers were presented for dose-response.

The analyses of active comparator, ranitidine versus famotidine, showed elevated relative risks for all 5 cancers: liver (1.22, 95% CI 1.06-1.40); esophageal (1.19, 95% CI 0.82-1.72); stomach (1.19, 95% CI 0.95-1.49); pancreas (1.25, 95% CI 0.90-1.73); bladder (1.03, 95% CI 0.80-1.33). These relative risks are similar to those for ranitidine versus all non-ranitidine users. More of the confidence intervals include 1.0, likely because the matching on famotidine reduced sample size. For the ranitidine versus PPI analysis (limited to liver cancer, likely because of small number of PPI users), the risk for liver cancer in ranitidine users was both higher than nonusers who had used PPIs and in those who had not.

There were several strengths to this study:

The study used a very large database of electronic health information including prescription data for Taiwanese individuals, which represents 99% of the Taiwan population. The database, begun in 2002, contains data from the entire single-payer national health system in Taiwan that was begun in 1995.(Hsieh et al. 2019) Since the database covers the entire population of Taiwan, this is a population-based cohort study, a considerable strength.

The study compared ranitidine users to nonusers for the primary analyses, which reduces the chance of bias from active comparators if the active comparators are themselves linked to cancer risk. However, to address the issue of indication bias, the researchers also did comparisons to famotidine users and to PPI users. That elevated risks for several cancers were found for all three analyses strongly support the validity of the study findings.

The cancer outcomes were retrieved from "formal cancer registries" which improve the accuracy of cancer diagnoses and reduce the chance of missing diagnoses.

There are several limitations to the study:

The investigators selected a subset of ranitidine users, matched them to nonusers, and followed for up to 18 years to observe cancer incidence in each cohort. This length of time, resulted in large numbers of patients with specific cancers in either of the two cohorts, but numbers were lower for more rare cancers (e.g., 101 ranitidine users and 82 non-users developed esophageal cancer). This hindered the study's power to detect statistically significant associations for some specific cancers. Furthermore, the average follow-up time of 9-10 years may not be sufficient to account for latency periods of some cancers in some patients. This will result in nonspecific misclassification, which biases the relative risk toward the null value of 1.0. In other words, the relative risk will be underestimated.

There was no information on ranitidine (or the comparator drugs for the sub-analyses with famotidine and PPI users) over-the-counter use patterns in Taiwan. If they are freely available, the lack of data would underestimate exposure. Furthermore, there are no data on whether or not the patients took the

medication as prescribed. All of these sources of error fall under the category of nondifferential misclassification, and would be expected to bias the relative risk toward the null.

While the Wang et al. paper presented data on risk by dose for than liver, lung, and pancreas cancers, no dose-response data were provided for bladder or esophageal cancers. While not required for causation, dose-response data is a key construct to consider for causal analyses.

Several potential confounding variables were not available (e.g., smoking, alcohol use). This lack of confounding variables can bias the relative risk in either direction.

Population studied:

This study used data from a very large electronic health record database that covered the entire population of Taiwan, and therefore had the potential to be highly representative of that population. However, once ranitidine and famotidine users were identified, many were excluded, resulting in two cohorts matched on age, sex, Charlson comorbidity index, hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, specific medications (aspirin, statins, angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, glucocorticoids, selective serotonin reuptake inhibitors), and antiviral therapy for hepatitis B or C virus infection), and the index date (since nonusers were assigned their matched ranitidine users' index dates). While some of these matching variables are appropriate (age, sex, index date), matching on all of the listed diseases and medications reduced the numbers of ranitidine cohort members available, reduced the numbers of cases, and decreased the chance of determining statistically significant associations.

For sub-analysis comparing ranitidine users to famotidine users: The study selected a subset of individuals who had been prescribed either ranitidine, or as comparator, another H2 blocker (famotidine) between 2000-2018. Famotidine and ranitidine have similar clinical efficacy, and therefore it is not clear why one is chosen over the other by prescribing physicians. If the reason for choice is because of insurance coverage or cost, there may be imbalance between ranitidine and famotidine user groups on related variables such as general health, employment status, or socioeconomic status.

Exposure measurement:

The Taiwan National Health Insurance Research Database contains health claims data for the entire population of Taiwan. The database also includes details of prescriptions dispensed at contracted pharmacies. The study therefore included data on dose of the medications as well as cumulative length of use. The study did not provide information on patient adherence to study medications as prescribed. The study did not identify diagnoses or symptoms for which ranitidine (or for the sub-analyses - famotidine or PPI) medications were prescribed. If famotidine or PPI users differed from ranitidine users on underlying diagnoses, general health, insurance status, socioeconomic status, or other risk factors for cancer, the results could be biased.

The investigators addressed crossover of medications in only a limited way, by eliminating any patients who had received a prescription for ranitidine or famotidine one year prior to index date (which ranged from 2000-2018). This did not adequately address the issue of whether patients in the famotidine cohort had previously used ranitidine. If famotidine users had previously used ranitidine, the study results would be biased toward the null value of 1.0. A similar issue is whether patients in either cohort had used proton pump inhibitors at any time. These medications, commonly prescribed for patients with the same conditions as for patients who have used H2 blockers, have been linked to increased risk for several cancers, and should have been adjusted for in analyses.(Abrahami et al. 2021; Seo et al. 2021; Zeng et al. 2021)

Outcomes measurement:

The outcomes, defined by ICD-9 and ICD-10 codes for multiple primary malignant neoplasms of the liver, oral cavity, esophagus, stomach, colon, rectum, pancreas, lung, bone, bladder, kidney, thyroid, skin, breast in females, uterus, cervix, ovary, and prostate. With a database this large, it is concerning that subtypes of these cancers were not analyzed, as cancer risk can vary by subtype.

Data on Covariates – Confounders and Effect Modifiers:

The covariates used in analyses were from linked electronic health records and a survey of the entire population. Ranitidine users and nonusers were matched on age, sex, Charlson comorbidity index,

hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, specific medications (aspirin, statins, angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, glucocorticoids, selective serotonin reuptake inhibitors), and antiviral therapy for hepatitis B or C virus infection), and the index date. No validation studies were referenced for these variables. However, a review publication on the Taiwan database shows high validation for some diseases but low for some.(Hsieh et al. 2019) The authors state that additional potential confounders (smoking, alcohol) were not available in the database.

Sample Size:

The numbers of patients prescribed ranitidine (290,990) was very large, and the numbers of cancer cases in this groups would have been expected to be large. The investigators correctly eliminated most of the ranitidine users because of exclusion criteria (age under 40, diagnosed cancer before ranitidine first prescription, used ranitidine less than 3 months, follow-up period less than one year). The resulting cohort of 75,715 was smaller, and was reduced even further with matching to nonusers on multiple medication and disease variables. The relatively small sample sizes for some cancers adversely affected the study's ability to detect statistically significant results for some cancers, although many of the relative risks were elevated with confidence intervals that did not include 1.0, indicating increased risk of several specific cancers with use of ranitidine.

Study Conduct:

The data were already collected before this study was conceived. No validation information was provided for the ranitidine (or comparator) exposure measurements, cancer outcomes, or covariates (although the Hsieh publication provided validation information for diseases including excellent validity for cancer)(Hsieh et al. 2019). Ranitidine use between 2000-2018 was determined, and patients were followed for cancer occurrence between 2000 and 2018. Therefore, the maximum follow-up was 18 years, which was longer than most of the other ranitidine-cancer epidemiology database studies. Furthermore, the investigators presented several graphs showing increasing risk with ranitidine over time compared with nonusers, which strongly supports that ranitidine increases risk for several cancers.

Data Analyses and Interpretation:

Statistical analyses were performed using a Cox proportional hazards regression model. This type of regression model is used to adjust for multiple covariates. Propensity score matching was used to aid in the regression modelling, but no trimming of patients was done, which ensures that all cancer cases were included. The covariates were the same as those chosen for matching. The results showed several hazard ratios (relative risks) for risk of specific cancers in ranitidine vs. non- users (relative risks) that were greater than 1.0, including all 5 of the cancers of interest in this litigation (liver, esophagus, stomach, pancreas, bladder). Two had confidence intervals that included 1.0, likely due to numbers of cases of specific cancers.

Effect of the Wang et al. Study on my Causation Opinions

While the Wang et al. study has some of the same weaknesses as the other studies reviewed in my expert report (Iwagami et al. 2021; Yoon et al. 2021; Kantor et al. 2021; Kim, Lee, et al. 2021; Kim, Wang, et al. 2021; Adami et al. 2021; Nørgaard et al. 2021; Habel, Levin, and Friedman 2000; Cardwell et al. 2021; McDowell et al. 2021; Kumar, Goldberg, and Kaplan 2021), it uses methodology that corrects for many of the weaknesses in these studies: 1) Cancer diagnoses: Unlike several of the other electronic insurance claims databases, the Wang et al. study uses data from cancer registries which improves capture and accuracy of cancer diagnoses. 2) Length of follow-up: This study followed patients for up to 18 years (with a median follow-up of almost 9 years). This is longer median follow-up than all of the other studies except the Adami et al. and Norgaard et al. studies from the Danish databases, but the maximum follow-up of 18 years in Wang et al. was identical to that of the Adami et al. and Norgaard et al. studies. Furthermore, by plotting graphs separately of cancer incidence in ranitidine users and nonusers, the picture of cancer causation increasing over time is clear: at the beginning of follow-up, the ranitidine and nonuser cancer incidences are similar, but the graphs diverge more and more over follow-up. 3) Use of propensity score matching: While Wang et al. use propensity score matching to aid in multivariate regression analyses, it is important to note that they did not perform “trimming” which is where cancer cases are removed if the exposed and unexposed cohorts cannot be matched on a set of variables. 4) Prescriptions do not equal medication ingestion: The medication database included information on dispensed medications, unlike many of the electronic health databases which only had prescriptions. 5) Dose-response data: Many of the other studies only had “ever” versus “never”

information. In contrast, Wang et al. had information on dose prescribed, and used that and length of prescriptions to create a defined daily dose variable (based on the World Health Organization defined daily dose of 300 mg for ranitidine). Wang et al. categorized patients into four levels of defined daily dose, and calculated relative risks for each level of defined daily dose compared with nonusers, to determine dose-response relationships. 6) Potential for indication bias: Wang et al. used several methods to address potential indication bias. First, they used a "wash-out" where they did not count medication use in the year prior to cancer diagnosis. This ensures that patients taking ranitidine (or comparator) are not using the drug specifically to treat the early symptoms of that cancer. Second, they examined associations between ranitidine use and specific cancer risk comparing ranitidine users to active comparators—the H2 blocker—famotidine, and PPIs.

Given these improved methodologies in the Wang et al. study, it strengthened my causal analyses. Of note, the Wang et al. paper also referenced other sources of NDMA as evidence of the effect of ranitidine with its component NDMA on risk of cancer, including some of the occupational and dietary sources that I included in my expert report.(Loh et al. 2011; Song, Wu, and Guan 2015; Hidajat et al. 2020)

Liver cancer: The relative risk of 1.22 (95% CI 1.09-1.36) is in the middle range of the five other ranitidine cancer epidemiologic studies. Therefore, Wang et al. is consistent with the other studies. The graph showing latency effects on the association between ranitidine use and risk for liver cancer clearly shows evidence of causation. Furthermore, there was a clear dose-response relationship between ranitidine use and risk for liver cancer with increasing relative risks with each increasing level of dose to a relative risk of 1.42 at the highest defined daily doses (with a confidence interval that excludes 1.0). This study strengthens several Bradford Hill criteria for liver cancer, including strength of associations, consistency between studies, and dose-response. This strengthens my causation opinion that ranitidine can cause liver cancer.

Stomach cancer: The relative risk of 1.26 (95% CI 1.05-1.52) lies in the middle range of relative risks seen for the other ranitidine-cancer epidemiologic studies reviewed for my report. The graph showing latency effects on the association between ranitidine use and risk for stomach cancer clearly shows evidence of causation. The dose-response analyses shows the highest relative risk (1.33) at the highest grade of exposure (over 360 defined daily doses). This study strengthens several Bradford Hill criteria for stomach

cancer, including strength of associations, consistency between studies, and dose-response. This strengthens my causation opinion that ranitidine use can cause stomach cancer.

Pancreas cancer: The relative risk of 1.35 (95% CI 1.03-1.77) lies in the middle range of relative risks seen for the other ranitidine-cancer epidemiologic studies reviewed for my report. Therefore, Wang et al. is consistent with the other studies. The graph showing latency effects on the association between ranitidine use and risk for pancreas cancer clearly shows evidence of causation. There were only 93 pancreas cancers in nonusers and 121 cases in ranitidine users. When the patients were subdivided into four levels of defined daily doses, the resulting small numbers would lead to unstable relative risks and statistical tests. This study strengthens Bradford Hill criteria for pancreas cancer, including strength of associations and consistency between studies. This strengthens my causation opinion that ranitidine use can cause pancreas cancer.

Esophageal cancer: The relative risk of 1.27 (95% CI 0.95-1.7) is consistent with the other ranitidine epidemiology studies, and lies in the middle of the other studies' relative risks. This study strengthens Bradford Hill criteria for esophageal cancer, including strength of associations and consistency between studies. This strengthens my causation opinion that ranitidine use can cause esophageal cancer.

Bladder cancer: While the relative risk for bladder cancer in Wang et al. (1.06, 95% CI 0.86-1.3) was lower than in most of the other ranitidine-cancer epidemiology studies, it showed a 6% increase in risk of bladder cancer in ranitidine users, so it is consistent with the other studies. Therefore, it does not change my causal opinion that ranitidine use can cause bladder cancer.

Ranitidine Dose Level that Can Cause Cancer

(Note –this section was included in my expert report beginning on page 286. It is repeated here, with the addition of information from the Wang et al. paper in the last paragraph.)

My causal analyses above included information about ranitidine "dose," primarily in terms of dose-response relationships. Many studies did not include information about specific pill doses or doses per day used. However, there is some information that is informative, and is summarized below.

Several epidemiologic studies measured the association between amount of ranitidine use and risk for various cancers (Table 2). The method for measuring amount varied among studies. Methods of classifying "dose" of ranitidine included: milligrams of ranitidine per pill, number of pills per day, and duration of use. Typical doses of ranitidine varied by indication for the medication (e.g. acute and maintenance therapies for gastric ulcer acute healing, esophagitis, gastroesophageal reflux disease, and others).

Some studies used the World Health Organization's Defined Daily Dose (DDD) to measure amount of ranitidine exposure. The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults, as assigned by the World Health Organization (https://www.who.int/tools/atc-ddd-toolkit/about-ddd accessed 8/24/21) The DDD for ranitidine (for peptic ulcer) is .3 grams (300 mg) (https://www.whocc.no/atc_ddd_index/?code=A02BA02) (accessed 1/20/22).

Several studies used the number of prescriptions as "dose" of exposure. However, the length of prescriptions varied (and often were not reported), as did dose on the prescription (which often was not reported).

A review of the available literature provides evidence that short-term use of ranitidine (such as use of 300 mg ranitidine over a period of 1-6 months) increases risks for cancers of the bladder, stomach, and liver. In particular, Cardwell et al. showed that as little as 1-182 DDD (WHO defined daily dose) increased risk of bladder cancer by 18% (relative risk 1.18, 95% CI 0.98-1.42). (Cardwell et al. 2021) (Since DDD for ranitidine is for 300 mg/day – see above - this indicates 6 months use of 300 mg/day ranitidine or one year use of 150 mg/day ranitidine would increase risk by 18%). Pancreatic cancer was increased with administration of 1- 5 prescriptions (with length of prescriptions suggestive of 28 days but not specified in the publication), (but risk was not further elevated with 6 or more prescriptions). Esophageal cancer risk was increased by 15% with at least 5 prescriptions, and by 53% with at least 10 prescriptions after follow-up for at least 10 years.

The most recent study, Wang et al., analyzed the association between ranitidine dose (defined daily dose, DDD) and risks for 4 cancers: liver, stomach, pancreas, and lung. Liver cancer showed a clear trend to increasing risk with increasing ranitidine DDD; the highest category (greater than 360 DDD) increased

risk by 42% (95% CI 1.22-1.66, p<0.001). Stomach cancer risk also was highest in the highest DDD category of ranitidine dose (relative risk 1.33, 95% CI 1.02-1.74). Pancreas cancer risk was elevated for 3 of the 4 categories of DDD, but the highest was the lowest dose category (DDD 90-180). It is important to note that DDD combines dose and duration of use into one variable. A patient classified as 360 DDD could have taking 300 mg ranitidine daily for a year, or 150 mg daily for 2 years, or 75 mg daily for 4 years. DDD is a good measure of total duration, but does not separate out pill dose and duration of use. Two ranitidine-cancer epidemiology studies have information concerning cumulative dose necessary to reach a statistically significant increased risk for specific cancers. Cardwell et. al. found that 3 years of ranitidine use (DDD or 300 mg/day) showed a statistically significant increased risk of bladder cancer when compared to one year use. The Wang et. al. study found that 1 year of ranitidine use (DDD or 300 mg/day) was associated with a statistically significant increased risk of liver cancer and stomach cancer, compared to shorter use. Therefore, real world exposure to ranitidine (measured doses) have demonstrated a statistically significant increase in risk for bladder, liver and stomach cancers. (Note, the term "statistical significance" is no longer used by many epidemiologists and statisticians. This has been debated throughout the various reports and depositions in this case. For the purpose of this paragraph, I use statistical significance as shorthand for a p value being less than 0.05 or a confidence interval that does not include 1.0).

Conclusion

For the reasons discussed in this supplemental report, the study by Wang et al. provides additional evidence supporting and strengthening my causation opinions. In conclusion, it is my professional opinion, stated to a medical and scientific degree of certainty, that based on the totality of the evidence, which includes epidemiological, biological, pathological and mechanistic data, ranitidine can cause cancers of the bladder, esophagus, liver, pancreas, and stomach.

Table 1: Comparators, Doses, Missing Data, and Follow-up in Studies on Ranitidine and Cancer Risk

(This is Table 4 from my expert report, with the study by Wang et al. added)

Study	Source of data	Years of medication use included[a]	Prescription vs. Dispensed Medication Data	Over the Counter Use Included or Relevant?	Ranitidine vs H2 blocker	Ranitidine vs Proton Pump Inhibitor	Ranitidine vs Nonusers	Long-term ranitidine use[b]	Length of follow-up[c]
(Wang et al. 2022)	Taiwan National Health Insurance Research Database	2000-2018	Dispensed	No OTC data provided	Yes (ranitidine vs famotidine)	Yes (ranitidine vs any PPI)	Yes (ranitidine vs nonusers)	Defined daily dose used for dose-response analysis	Ranitidine: Mean-9.56 years Median-8.42 years Nonusers: Mean-9.7 years Median-8.58 years Range: 0-18 years
(Iwagami et al. 2021) Cancers: Stomach Bladder Pancreas Also: Colorectal Lung Malignant melanoma Breast Uterine Prostate	Japanese electronic health records databases	2005-2018 (Combined ranitidine & nizatidine users)	Prescribed & Dispensed	No OTC data provided	Combined ranitidine & nizatidine vs other H2 blockers	No	No	Not reported for specific cancers	Median (interquartile range): R & N: 2.4 (1.1-4.5) Other H2 blockers: 2.3 (.9-4.2)

Kidney Other cancers									
(Yoon et al. 2021) Cancers: Bladder Liver Stomach Also: Kidney Prostate Breast Uterus Lung Colorectal Thyroid Biliary	South Korea electronic health records database	2009-2011 (excluded those using 2007-2008)	Prescribed	No OTC data provided	Yes (vs famotidine)	No	Not reported for specific cancers	Ranitidine and famotidine users matched for cumulative exposure; RR for duration reported not reported for specific cancers	2009-11 to 2012-18
(Adami et al. 2021) Cancers: Pancreas Liver Stomach Esophageal	Danish electronic health records database, pharmacy registry, cancer registry	1996-2008	Dispensed	From 2002, half of ranitidine use OTC, versus almost none of comparators	Yes	Yes	No	≥ 10 prescriptions	Median (IQR): Ranitidine: 14 (10-18) Other H2 B: 16 (11-19) PPI: 12 (9-16)
(Nørgaard et al. 2021) Bladder cancer Also: Kidney cancer	Danish electronic health records database, pharmacy registry, cancer registry	1996-2008	Dispensed	From 2002, half of ranitidine use OTC, versus almost none of comparators	Yes	Yes	No	≥ 10 prescriptions	Median (IQR): Ranitidine: 14 (9-18) Other H2 B: 15 (7-19) PPI: 12 (5-16)
(Kumar, Goldberg, and Kaplan 2021)	Cohort, U.S. Veterans electronic health records	1998-2018	Prescribed	Not included but OTC provided	Yes	Yes	No	Not reported	Median 4.4 years, IQR 1.7–

Stomach cancer in *H. pylori* patients	database including pharmacy use			by VA at deep discounts, may decrease non-VA purchase					9.2 years
(Kim, Wang, et al. 2021) Cancers: Esophagus Stomach Liver Pancreas Also: Colorectal	IBM Explorys electronic health records database	2009-2018	Prescribed	Over-the-counter data missing	Yes	Yes	No	Not reported	1-10 years
(Kim, Lee, et al. 2021) Stomach cancer	Korean electronic health records database	2002-2008 (Combined ranitidine & nizatidine users)	Prescribed	No OTC data provided	Yes Combined ranitidine & nizatidine users vs other H2 users	No	Yes	Not reported	2002-8 to 2013
(Kantor et al. 2021) Cancers: Bladder Liver Also: Colorectal Lung Breast Prostate Kidney Ovary	Cohort (UK Biobank), cancer registry	2006-2010	Self-report of use in 4 week period	Self-report could have included OTC use	No	Yes	Yes	Not reported	Median 6.7 years
(McDowell et al. 2021) Pancreas cancer	Scottish general practice electronic health records database, pharmacy registry, cancer registry	1993-2010	Prescribed	Not included (but only 10% of ranitidine purchased OTC in UK)	No	No	Yes	6 or more prescriptions	Nested case-control study Cases diagnosed 1999-2011; prescriptions

									1993-1 year before diagnosis
(Cardwell et al. 2021) Bladder cancer	Scottish general practice electronic health records database	1993-2010	Prescribed	Not included (but only 10% of ranitidine purchased OTC in UK)	Yes (sensitivity analyses)	Yes (sensitivity analyses)	Yes (main analyses)	36 or more prescriptions	Nested case-control study Cases diagnosed 1999-2011; prescriptions 1993-1 year before diagnosis
(Liu et al. 2020) Stomach cancer	Scottish general practice electronic health records database	1993-2010	Prescribed	Not included (but only 10% of ranitidine purchased OTC in UK)	No	No	Yes	> 1095 DDD (~ > 3 years)	Nested case-control study Cases diagnosed 1999-2011; prescriptions 1993 - 1 year before diagnosis
(Tran et al. 2018) Liver cancer	Cohort (UK Biobank), cancer registry	2006-2010	Self-report of use in 4 week period	Self-report could have included OTC use	No	No	Yes	Not reported	Median 5.6 years (range 1-8.6 years)
(Tran et al. 2018) Liver cancer	Scottish general practice electronic health records	1993-2010	Prescribed	Not included (but only 10% of ranitidine	No	No	Yes	Not reported	Nested case-control study Cases

	database			purchased OTC in UK)					diagnosed 1999-2011; prescriptions 1993 - 1 year before diagnosis
(Tan et al. 2018) Esophageal cancer in Barrett's esophagus patients	Cohort, U.S. Veterans electronic health records database including pharmacy use	2003-2011	Dispensed	Not included but OTC provided by VA at deep discounts, may decrease non-VA purchase	No	No	Yes	DDD > 150	Nested case-control study within cohort of Barrett's Esophagus patients diagnosed 2004-9; esophageal cases diagnosed in cohort through 2011
(Habel, Levin, and Friedman 2000) Cancers: Bladder/kidney Pancreas Liver Stomach Esophageal Also: Prostate Breast	U.S. Kaiser computerized pharmacy and electronic health record databases; linkages to SEER cancer registries	1982-1985	Dispensed	OTC not available during time of data collection	No	No	Yes	Only reported for breast and prostate cancers	1982-85 to 1995

Uterus Ovary Lung Colorectal Melanoma Lymphoma/ myeloma/ leukemia									

Table 2: Relative risks of specific cancers associated with ranitidine use by "dose"

(This is Table 5 from my expert report, with the study by Wang et al. added)

Study	Year	Definition of "dose"	Cancers	Source of medication data
(Wang et al. 2022)	2022	DDD: 90-180 DDD 181-270 DDD 271-360 DDD Over 360 DDD	liver, stomach, esophagus, pancreas, bladder plus other specific cancers Elevated risk starts with: Liver 181-270 DDD (highest with >360) Stomach 90-180 DDD (highest with >360) Pancreas 90-180 DDD	Taiwan National Health Insurance Research Database
(Cardwell et al. 2021)	2021	DDD Number of prescriptions (? 28 days' length?)	Bladder RR 1.18 with 1-182 DDD (corresponds to 300 mg for up to ½ year or 150 mg for up to 1 year)	Prescriptions from primary care records (Scotland)
(Kantor et al. 2020)	2021	use $\geq$ 4 weeks="user" No dose information	Multiple	UK biobank
(Yoon et al. 2021)	2021	Cumulative duration (only for all cancers combined) Study included only ranitidine users with > 10,800 cumulative intake and famotidine users with > 14,400 mg	Multiple. Cancer risk overall not increased with increased duration.	South Korea national health insurance database

		intake.		
(Shin et al. 2021)	2021	DDD All H2blockers combined (no ranitidine-specific data)	Stomach	Korean national health services prescription database
(Iwagami et al. 2021)	2020	DDD	All cancers combined (individual cancer analyzed as users/nonusers only); RR for all cancers combined ~ 1.0 regardless of DDD class	Japan medical claims database
(Liu et al. 2020)	2020	Scottish database: DDD (for all H2RA combined) UK Biobank: no dose information	Stomach RR 1.44 with 1-183 DDD (corresponds to 300 mg for up to ½ year or 150 mg for up to 1 year)	Prescriptions from primary care records (Scotland) UK Biobank
(McDowell et al. 2021)	2020	Number of prescriptions "low usage": 1-5 prescriptions "higher usage": ≥ 6	Pancreas RR 1.37 with "lower usage"	Prescriptions from primary care records (Scotland)
(Tran et al. 2018)	2018	Scottish database: DDD (for all H2RA combined) Number prescriptions UK Biobank: no dose information for ranitidine	Liver cancer RR 1.24 at 1-193 DDD RR 1.21 at 1-11 prescriptions	Prescriptions from primary care records (Scotland) UK Biobank
(Tan et al. 2018)	2018	DDD	Esophageal RR 3.0 at DDD ≤ 150 mg	US Veterans pharmacy database
(Habel, Levin, and Friedman 2000)	2000	≥1 prescription classified as "user", no dose	Multiple	HMO pharmacy database
Adami (Adami et al. 2021)	2021 (corrected version March 2022)	Number of prescriptions (dose and length of prescriptions not defined). Analyzed data to dichotomized to "at least 5 prescriptions" vs	Comparing ranitidine to other H2 blockers: Esophageal: at least 5 prescriptions, RR	Danish national prescription registry (noted that percent of ranitidine DDD

		not and "at least 10 prescriptions" vs not)	1.34 Stomach: at least 5 prescriptions, RR 1.15 Esophageal: at least 10 prescriptions followed for at least 10 years, RR 1.32 Stomach: at least 10 prescriptions followed for at least 10 years, RR 1.53 <u>Comparing ranitidine to PPI's:</u> Esophageal: at least 10 prescriptions, RR 1.32 after 10 years' follow-up Stomach: at least 10 prescriptions, RR 1.53 after 10 years' follow-up	sold by prescription by year was: 1999 84% 2004-11 50% 2012-17 20%

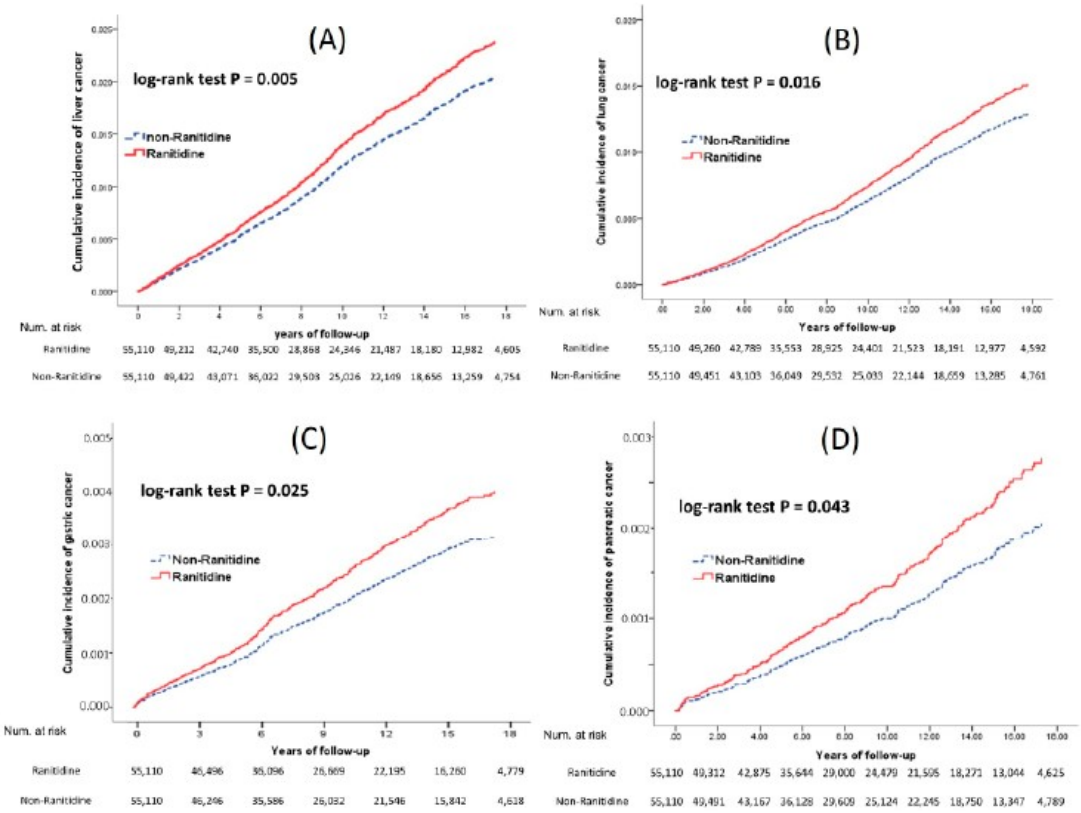
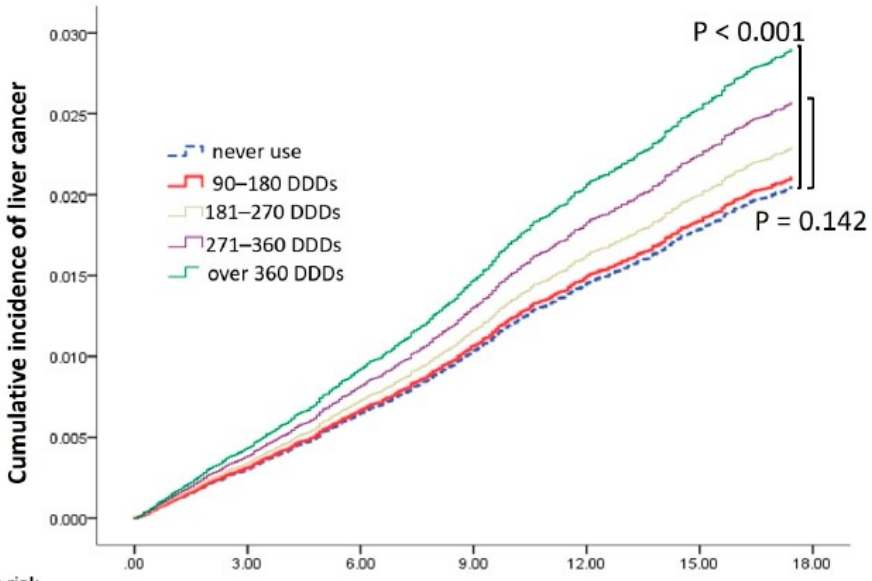


Figure 3. Cumulative incidences of single cancers after adjustment for competing risks. (**A**) Liver cancer, (**B**) lung cancer, (**C**) gastric cancer, and (**D**) pancreatic cancer.



Num. at risk							
over 360 DDDs	14,787	12,546	9,009	5,733	4,611	3,349	1,098
271–360 DDDs	5,289	4,334	3,316	2,412	1,973	1,472	471
181–270 DDDs	10,844	9,202	7,354	5,668	4,741	3,531	985
90–180 DDDs	24,190	20,098	15,821	12,151	10,162	7,449	2,051
never use	55,110	46,420	36,022	26,605	22,149	16,208	4,754

Figure 4. Cumulative incidences of liver cancer for different prescription durations after adjustment for competing risks. Abbreviations: DDDs, defined daily doses.

Table 3. Estimates for the association between ranitidine use duration and cancer risk compared with non-ranitidine use by multivariate Cox proportional hazards regression.

	Liver Cancer	*p*	Gastric Cancer	*p*	Lung Cancer	*p*	Pancreatic Cancer	*p*
Never used	1.00		1.00		1.00		1.00	
90–180 DDDs *	1.03 (0.89–1.18)	0.690	1.26 (1.00–1.59)	0.049	1.25 (1.09–1.44)	0.002	1.64 (1.19–2.26)	0.003
181–270 DDDs	1.12 (0.93–1.34)	0.220	1.13 (0.82–1.54)	0.452	1.09 (0.90–1.32)	0.403	1.10 (0.69–1.77)	0.682
271–360 DDDs	1.26 (0.99–1.61)	0.064	1.27 (0.84–1.93)	0.252	1.31 (1.02–1.68)	0.032	0.92 (0.45–1.89)	0.816
Over 360 DDDs	1.42 (1.22–1.66)	<0.001	1.33 (1.02–1.74)	0.037	1.04 (0.87–1.24)	0.658	1.22 (0.80–1.85)	0.358

* Abbreviations: DDDs, defined daily doses.

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EXHIBIT C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION *THIS DOCUMENT RELATES TO ALL CASES*	MDL NO. 2924 20-MD-2924

SUPPLEMENTAL EXPERT REPORT

PATRICIA G. MOORMAN, MSPH, PHD

Date: October 3, 2022

Patricia G. Moorman, MSPH, PhD

Addendum to Expert Report of Patricia G. Moorman, Ph.D.

Re: Wang C, Chen I, Chen C, Tseng Y. Pharmacoepidemiologic research on N-nitrosodimethylamine-contaminated ranitidine use and long-term cancer risk: a population-based longitudinal cohort study. Int J Environ Res Public Health 2022, 19: 12469

Wang et al. [1]conducted a cohort study using data from Taiwan's National Health Insurance Database and a cross-sectional survey of Taiwan's population. Data were available from 2000 to 2018. They identified individuals who were first-time users of ranitidine and had received at least 90 defined daily doses (i.e., ranitidine 300 mg daily for at least 3 months). The comparison group comprised non-users of ranitidine matched to the ranitidine users on exact age, sex, Charlson comorbidity index score, certain co-morbid conditions and certain medications using propensity score matching. They also conducted analyses comparing ranitidine users to famotidine users and proton pump inhibitors (PPIs). No information was available for potential confounders such as smoking history, body mass index, alcohol consumption and certain gastrointestinal conditions. The analyses were restricted to individuals age $\geq$ 40 years with at least 1 year of follow-up.

A total of 55,110 ranitidine users and 55,110 non-users were included in the analysis. Mean follow-up time was 9.56 years for the ranitidine group and 9.70 for the non-ranitidine group. The investigators calculated cancer risk for all cancers combined and for 18 individual cancer sites. The analysis was based on 9,081 cancers (4,682 in the ranitidine group and 4,399 in the non-user comparison group). The multivariate-adjusted hazard ratio (HR) comparing ranitidine users to non-users for all cancer combined was 1.10 (95% CI 1.06-1.15). The HRs for the other cancer sites that were discussed in my prior report were: 1.22 (95% CI 1.09-1.36) for liver cancer (based on 711 vs. 619 cases in the ranitidine and comparison groups, respectively); 1.26 (95% CI 1.05-1.52) for gastric cancer (based on 255 vs. 210 cases in the ranitidine and comparison groups, respectively); 1.27 (95% CI 0.95-1.70) for esophageal cancer (based on 101 vs. 82 cases in the ranitidine and comparison groups, respectively); 1.35 (95% CI 1.03-1.77) for pancreatic cancer (based on 121 vs. 93 cases in the ranitidine and comparison groups, respectively) and 1.06 (95% CI 0.86-1.30) for bladder cancer (based on 181 vs. 177 cases in the ranitidine and comparison groups, respectively).

Dose response analyses were reported for liver, gastric and pancreatic cancer, using the categories of 90-180 DDDs, 181-270 DDDs, 271-360 DDDs, and >360 DDDs. The HRs for liver cancer showed increasing risk with increasing dose of ranitidine, with a HR of 1.42 (95% CI 1.22-1.66) for the highest exposure level. The HRs for gastric cancer also showed the highest risk with the highest exposure level (HR 1.33, 95% CI 1.02-1.74) but the dose-response trend was not as clear as for liver cancer. A clear dose-response trend was not apparent for pancreatic cancer.

In analysis comparing ranitidine users to famotidine users, the HRs (95% CIs) were 1.22 (1.06-1.40) for liver cancer, 1.19 (0.95-1.49) for gastric cancer, 1.19 (0.828-1.72) for esophageal cancer, 1.25 (0.90-1.73) for pancreatic cancer and 1.03 (0.80-1.33) for bladder cancer. A comparison between ranitidine users and PPI users was reported only for liver cancer, with a significantly higher risk for ranitidine users ($p<0.001$, HR not reported).

The strengths of this study include the use of a database with virtually complete coverage of the Taiwanese population that had information on all medical services, procedures and prescriptions. The follow-up period was longer than most of the other studies of ranitidine and cancer ([2-6], with a mean follow-up time of approximately 10 years, and a maximum follow-up period of 18 years. However, given that the latency period for the development of cancer can be decades, it is likely that with longer follow-up, a greater increase in risk would become apparent. The investigators presented Kaplan-Meier graphs showing the risk of liver, gastric and pancreatic cancer in the ranitidine and comparison groups over time. These graphs showed that the incidence curves for ranitidine and the comparison groups had greater separation with longer follow-up times, indicating that the cancer risk in the ranitidine group compared to the non-users or users of other acid-suppressing drugs was increasing over time. The greater risk with longer follow-up time also indicates that protopathic bias was unlikely to be an explanation for the increased risk observed for liver, gastric and pancreatic cancer.

Information on ranitidine dose and duration was available, and the investigators conducted dose-response analyses based on four categories of defined daily doses. Analyses were conducted that compared ranitidine users to both non-users and to users of famotidine or PPIs. The study population was restricted to individuals aged $\geq$ 40 years, with a mean age of

66.8 years, therefore it included good representation of the ages when the cancers are most likely to be diagnosed. It also incorporated a new-user design with 1 year as the washout period to address protopathic bias.

The study also had limitations. Similar to other administrative databases, information was not available for some potential confounders including smoking history, alcohol use and some medical conditions. There was likely some misclassification of ranitidine exposure, due to the lack of information on non-prescription use of ranitidine. While the investigators noted this as a limitation, they did not give an estimate of the proportion of ranitidine sold without a prescription in Taiwan. If there was similar use of non-prescription ranitidine in the groups being compared, the misclassification would be considered non-differential and lead to an underestimate of the relative risk. There was also the potential for misclassification if some of the individuals who were in the non-ranitidine user group had used ranitidine prior to the year 2000, which was the start date of national insurance database. If people who had used ranitidine prior to 2000 were included in the non-user group, it would tend to underestimate the risk associated with ranitidine use.

Although the dose-response analysis conducted in this study was more detailed than in most of the other ranitidine and cancer studies, the investigators still did not provide information on the risk associated with very long-term use, as the highest category of use was >360 DDDs (or approximately one year of use or longer). Long-term users (i.e., those with greater than 5 years or greater than 10 years of ranitidine use) would have been included in the highest duration category, however if the risk markedly increased with long-term use, it would not have been apparent in these analyses that also included individuals with shorter term use. This study showed statistically significant increases in liver and gastric cancer with $\geq$ 1 year of ranitidine use (at 300 mg per day). The only other study with detailed dose-response analyses, Cardwell, et al.,[7], reported a statistically significant increased risk for bladder cancer risk with 3 years of ranitidine use (300mg per day). Thus an association between ranitidine use and increased risk of bladder, gastric and liver cancer have been demonstrated at typical doses of 300mg daily for 3 years and 1 year.

As noted above, this study had some of the limitations discussed in my prior reports for other studies of ranitidine use and cancer (lack of information on smoking, alcohol, and OTC use) which as with the others, is attributable to the database limitations. However, the study had several strengths not present in the other studies. Notably, this study was able to provide more meaningful evidence of dose response because there was more dose and duration information, it had longer follow-up than many of the other studies, it presented comparisons of ranitidine use versus non-use and comparisons of ranitidine use versus use of other acid suppressants, and the study population was age-appropriate for studying cancers that are typically diagnosed in older adults.

Overall, the study's strengths, including its dose-response analysis, its presentation of cancer risks over time, and its comparison of ranitidine users to both non-users and to users of other acid-suppressing drugs, outweighed its limitations and therefore I gave it considerable weight in my causation analysis, weighting it more strongly than the Iwagami, Yoon, Adami, Norgaard, Kantor, Kim, S and Kim, Y studies.[2-6, 8, 9] Its findings of significantly increased risk of liver, gastric and pancreatic cancer and increased risk of esophageal cancer, although not statistically significant, strengthens the causality opinions expressed in my prior report.

1. Wang, C., Chen, I., Chen, C., Tseng, Y., *Pharmacoepidemiologic research on N-nitrosodimethylamine-contaminated ranitidine use and long-term cancer risk: a population-based longitudinal cohort study.* . Int J Environ Research Public Health, 2022. **19**: p. 12469.
2. Iwagami, M., et al., *Risk of Cancer in Association with Ranitidine and Nizatidine vs Other H2 Blockers: Analysis of the Japan Medical Data Center Claims Database 2005-2018.* Drug Saf, 2021. **44**(3): p. 361-371.
3. Yoon, H.J., et al., *Risk of Cancer Following the Use of N-Nitrosodimethylamine (NDMA) Contaminated Ranitidine Products: A Nationwide Cohort Study in South Korea.* J Clin Med, 2021. **10**(1).
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6. Kim, S., et al., *Effect of Ranitidine Intake on the Risk of Gastric Cancer Development.* Healthcare (Basel), 2021. **9**(8).
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8. Adami, H.-O.A., I.T.; Helde-Jorgensen, U.; Chang, E.; Norgaard, M.; Sorensen, H.T., *Ranitidine use and risk of upper gastrointestinal cancers.* 2021.
9. Norgaard, M., et al., *Ranitidine and Risk of Bladder and Kidney Cancer: A Population-Based Cohort Study.* Cancer Epidemiol Biomarkers Prev, 2021.

EXHIBIT D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION *THIS DOCUMENT RELATES TO ALL CASES*	MDL NO. 2924 20-MD-2924

SUPPLEMENTAL REPORT

ANDREW GALE SALMON M.A., D.PHIL., C.CHEM., M.R.S.C.

Date: October 4, 2022

Andrew Gale Salmon M.A., D.Phil., C.Chem., M.R.S.C

Wang C-H, I-I Chen, Chen C-H, and Tseng Y-T .(2022). Pharmacoepidemiological Research on N-Nitrosodimethylamine Contaminated Ranitidine Use and Long-Term Cancer Risk: A Population-Based Longitudinal Cohort Study. Int. J. Environ. Res. Public Health **19**, 12469.

Wang et al. (2022) report a population-based cohort study of cancer among ranitidine users. 55,110 patients who received ranitidine between January 2000 and December 2018 were identified from the Taiwan National Health Insurance Research Database. These were statistically matched to an equivalent number of non-ranitidine users in consideration of age, sex, comorbidity index, and comorbidities, including hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, and chronic kidney disease, and the index date. The total doses for each ranitidine prescription during the follow-up period were determined as the number of defined daily doses (DDDs) where one DDD of ranitidine was 300 mg/day (per WHO).

Patients prescribed ranitidine at least 90 DDDs (treated with 300 mg ranitidine daily for 3 months) were assigned to the ranitidine cohort, whereas those who never used ranitidine belonged to the non-ranitidine cohort. Patients younger than 40 years, with a cancer diagnosis before the index date, ranitidine use <90 DDDs, or follow-up less than 1 year were excluded from the cohort. The index date for each ranitidine user was defined as the date of their first prescription, and for their corresponding matched comparison group, the index date was set to that of their matched individual with ranitidine use. All patients' prescriptions, diagnostic outcomes, and deaths were ascertained from their index date to until December 31, 2018. The follow-up period (mean ±SD) was 9.56 ± 5.96 (median: 8.42) years for the ranitidine cohort and 9.70 ± 5.96 (median: 8.58) years for the non-ranitidine cohort. Parallel groups of ranitidine users and famotidine users (N= 35269) were also identified in the cohort.

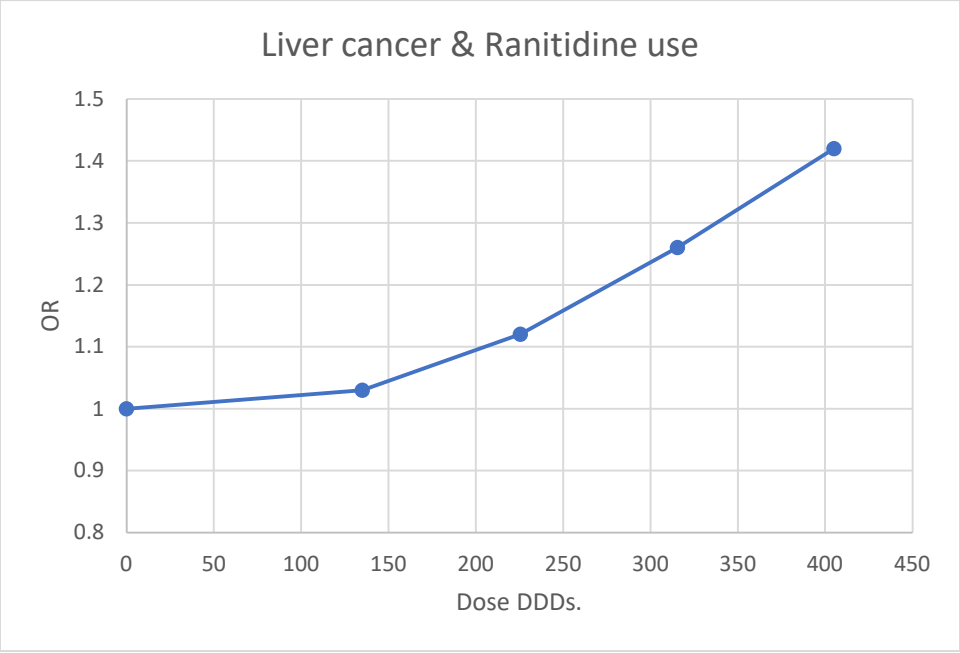
A multivariate analysis of observed outcomes was performed using several standard methodologies and sensitivity analyses to evaluate the reliability of the results. The ranitidine cohort showed a significantly higher prevalence of liver cancer (1.1% vs. 1.3%; p = 0.012), gastric cancer (0.4% vs. 0.5%; p = 0.037), and lung cancer (1.0% vs. 1.2%; p = 0.033) and a higher overall cancer rate (8.0% vs. 8.5%; p = 0.001) than the non-ranitidine cohort. The ranitidine cohort showed a non-statistically significant higher prevalence of esophageal cancer (0.1% vs. 0.2%) and no increased prevalence for bladder cancer (0.3% vs. 0.3%). Ranitidine use was associated with increased cumulative incidence rates for overall cancer [Hazard ratio (HR) 1.10; 95% CI, 1.06–1.15], liver cancer (HR, 1.22; 95% CI, 1.09–1.36), gastric cancer (HR, 1.26; 95% CI, 1.05–1.52), pancreatic cancer (HR, 1.35; 95% CI, 1.03–1.77), and lung cancer (HR, 1.17; 95% CI, 1.05–1.31) compared with non-ranitidine use. 14 other cancers were examined for which statistically significant associations with ranitidine use were not observed, although for some an elevated central estimate of the hazard ratio was reported (including findings for bladder cancer of HR, 1.06; 95% CI, 0.86-1.30 and esophageal cancer of HR, 1.27; 95% CI, 0.95-1.70).

Incidence of liver cancer showed a relationship with cumulative dose of ranitidine (as number of DDDs prescribed). This dose response is very clearly shown below and in the statistics presented by the study authors. Cumulative exposure in DDDs or mg was estimated based on mean values for each group (with the top group mean estimated based on the reported group ranges for the other groups).

DDD range L	DDD range H	DDD median	Dose mg	OR	increment in OR/mg
never		0	0	1	0
90	180	135	40500	1.03	7.407E-07
181	270	225.5	67650	1.12	1.774E-06
271	360	315.5	94650	1.26	2.747E-06
361	450 *	405.5	121650	1.42	3.453E-06

*estimated
1 DDD = 300 mg
mean slope 3.4949E-06
R^2 0.89662

The increment in OR for liver cancer per mg of cumulative exposure varies from 7.407×10^{-7} for the 90 to 180 DDD group to 3.453×10^{-6} for the >360 DDD group. There was an overall linear correlation between dose and odds ratio for liver cancer (mean slope = 3.5×10^{-6}, $R^2 = 0.90$).



A dose response is also shown by the data for gastric cancer, although this trend shows more scatter than that for liver cancer, potentially due to the lower incidence of gastric cancer (0.48 per 1000 person years) compared to liver cancer (1.35 per 1000 person years). Nevertheless, an overall trend is clearly discernable in the data:

DDD range L	DDD range H	DDD median	Dose mg	OR	Increment in OR/mg
never		0	0	1	0
90	180	135	40500	1.26	6.42E-06
181	270	225.5	67650	1.13	1.922E-06
271	360	315.5	94650	1.27	2.853E-06
361	450*	405.5	121650	1.33	2.713E-06

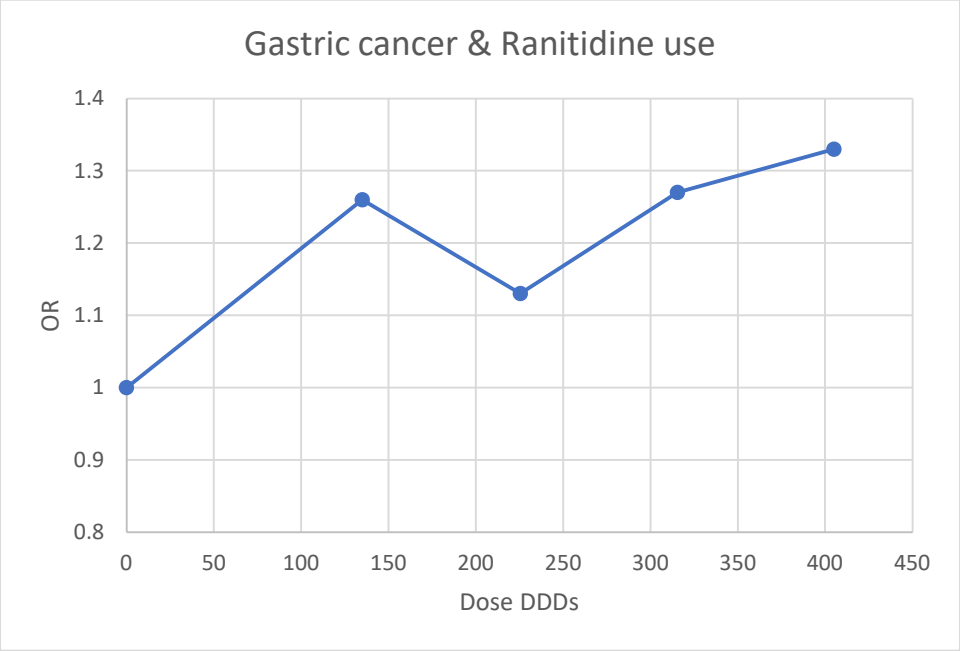
*estimated

1 DDD = 300 mg

mean slope 2.32983E-06

R^2 0.68898

The increment in OR for gastric cancer per mg of cumulative exposure varies from 1.92 x 10^{-6} for the 181 to 270 DDD group to 6.42 x 10^{-6} for the 90 to 180 DDD group. There was an overall linear correlation between dose and odds ratio for gastric cancer (mean slope = 2.3x 10^{-6}, R^2 = 0.69).



Users of ranitidine also showed higher incidence of liver cancer than users of famotidine in the paired comparison of these two groups of users (adjusted HR, 1.22; 95% CI, 1.06–1.40, p = 0.005). Incidence of liver cancers was also elevated in users of ranitidine compared to non-users without proton pump inhibitor use (adjusted HR, 1.16; 95% CI, 1.04–1.30, p = 0.006). Comparison of other cancer risks for users of ranitidine versus users of famotidine is as follows: esophageal cancer (adjusted HR, 1.19; 95% CI, 0.82-1.72), gastric cancer (adjusted HR, 1.19; 95% CI, 0.95-1.49), pancreas cancer (adjusted HR, 1.25; 95% CI, 0.90-1.73) and bladder cancer (adjusted HR, 1.03; 95% CI, 0.80-1.33).

The strengths of this study include the matched cohort design, large number of subjects and long duration of follow-up (median of 8.3 years and up to 18 years). The fact that the database from which the subjects were identified, and the survey of demographic, health and prescription use data were obtained, are part of a large national system covering a high proportion of the population of Taiwan is also a strength, making unbalanced selection of subjects from the general population unlikely. Unlike many previous studies of ranitidine use this study used a relatively objective and quantitative measure of cumulative exposure, based on the DDDs reported in the prescriptions received by the ranitidine users. Although still subject to some limitations such as partial compliance with prescriptions and over-the-counter use, these are much less problematic than broad categorical dose measures. Additional limitations included alcohol consumption and smoking data were not available, although given the carefully matched control group the chance of an extensive impact of these uncertainties may be small. The authors present a thorough and cautious statistical analysis using a variety of standard methodologies, and their findings for liver and gastric cancer are consistently supported in these analyses which is why I give this study greater weight.

Dose-response

The dose response relationship reported for liver and gastric cancer risk provides additional evidence to support the consistency and dose response Bradford Hill factors for these cancers. Of the previously described studies, Cardwell et al. (2021) is the other study which found statistically significant cancer incidence and dose response associated with use of ranitidine and bladder cancer, which also used the DDD as a quantitative dose measure (though it reported results for longer exposures of 1-3 years and more than 3 years). These new results by Wang et al. are an important further demonstration of the causal association between use of ranitidine containing NDMA and cancer.

The Cardwell et al. study found that at only 3 years of ranitidine usage (of 300 mg per day) there is a statistically significant increased risk of bladder cancer. The Wang study found that at only 1 year of ranitidine usage (of 300 mg per day) there is a statistically significant increased risk of liver cancer and gastric cancer. There are Zantac users who have used Zantac for at least 1 year or at least 3 years. Therefore, this study supports the conclusion that Zantac can cause cancer at doses ingested by the U.S. population.

In this case researchers observed consistent overall results for ranitidine users vs. non-users. This supports the conclusion based on a reasonable degree of scientific certainty that the cancer risk seen in ranitidine users is the consequence of the presence of the carcinogen NDMA in the ranitidine (which is absent from famotidine and PPIs), rather being related to the indication for medication use. In fact, that is precisely what the study authors concluded on page 12 after considering different alternative explanations: "However, the clear data from our real-world observational study strongly support the pathogenic role of NDMA contamination, given that long-term ranitidine use is associated with a higher likelihood of cancer development in ranitidine users compared to the control groups of non-ranitidine users who were treated with PPIs or famotidine."

Comparison of the dose of NDMA expected from ranitidine use in the study by Wang et al. with that from occupational exposure in the study by Hidajat produce broadly consistent estimates. Based on Emery's overall average NDMA content after consumer storage, the Wang study evaluated median cumulative exposure of 2.5 mg NDMA in the highest exposure group, finding an increased risk of the incidence of liver cancer of 42%. Hidajat's reference group (quartile I) had a similar median NDMA amount, meaning no increased risk would be detectable based on the study design. But moving from quartile I to quartile II (8.7 mg median), the mortality risk increased by 53% (almost, but not quite, statistically significant), and quartile III (15 mg median) had an increased mortality risk of 96%. The risk increases are not directly comparable, since the Hidajat study is of mortality which is necessarily a less sensitive measure of impact than the incidence reported by Wang. But these increases are broadly consistent, since the higher amount of NDMA in Hidajat produced a larger increased risk than the lower NDMA amount in Wang (and Hidajat's risk increase may have been larger still had it measured incidence rather than mortality). Wang found elevated odds ratios for bladder cancer (1.06) and esophageal cancer (1.27), but these did not achieve statistical significance in that study, likely due to the small number of cancer cases. For these cancers, my analysis relies on the alternative studies which provide statistically significant results (such as Keszei and Hidajat), although the observations by Wang are supportive rather than contradictory.

Associations

This study makes an important contribution to the data on cancer associated with ranitidine use. The significant associations observed in this study, and especially the positive dose-response relationships demonstrated for liver and gastric cancer, provide further direct support for my earlier conclusion based on a reasonable degree of scientific certainty that liver, gastric and pancreatic cancer are consequences of the exposure to the NDMA breakdown product in ranitidine. This is based on a review of the animal studies and mechanistic data on NDMA, review of epidemiological studies of NDMA exposure via occupational or dietary exposure, review of prior studies of ranitidine use, and measurement of NDMA levels in ranitidine initially and following handling and storage.

Bradford Hill

Further to my analysis of stomach cancer in relation to NDMA and ranitidine exposures according to the Bradford Hill methodology in my March 28, 2022 Report ("Report" which I will not duplicate here), the new finding by Wang et al. provide additional compelling evidence to support the strength and consistency of this association since it not only finds a statistically significant increase in overall stomach cancer in ranitidine users, but also demonstrates a dose response relationship which is a key finding in the Bradford Hill scheme of interpretation. This finding is also consistent with the reported findings of stomach cancer associated with NDMA exposure in various dietary studies and in the occupational study by Hidajat et al (2019), and the extensive data on animal carcinogenicity and mechanism of action for NDMA.

Similarly, when reviewing the evidence for liver cancer according to the Bradford Hill criteria discussed in my Report, the findings by Wang et al. add further compelling evidence to support the strength and consistency of the evidence for liver cancer, in that they found both a statistically significant increase in overall cancer incidence, and a very clear dose response relationship with ranitidine use. This is consistent with the dose response for liver cancer seen with occupational exposure to NDMA by Hidajat et al. (2019) and with the extensive data on animal carcinogenicity and mechanistic studies of NDMA.

Another influential finding by Wang et al. is of an association between pancreatic cancer and ranitidine use (HR, 1.35; 95% CI, 1.03–1.77). This adds further strength and consistency to my Bradford Hill analysis for pancreatic cancer discussed in my Report. In comparison to the studies assessing the association of pancreatic cancer and ranitidine discussed in my Report, the statistically significant finding by Wang et al. is an important addition to the data set. They were not able in this case to demonstrate a clear dose response, possibly due to the number of cases (121 in the ranitidine users), which is less than half the number of gastric cancers and less than one fifth of the liver cancer cases. The numbers for the higher doses in the pancreatic cohort were so low that p values were 0.682, 0.816 and 0.358 respectively indicating that the size of the cohort was too small to see a clear effect.

The evaluation of the association between bladder cancer and ranitidine use according to the Bradford Hill criteria in my Report relied, inter alia, on data from the Cardwell study which demonstrated a significant association and dose response for bladder cancer among ranitidine users. The study by Wang reported a modest increase in cases of bladder cancer in ranitidine users (181 vs. 177 in controls) but this was not statistically significant. The low number of overall cases, and the relatively high rate of bladder cancer in the controls compared to some of the other sites analyzed, possibly contributed to this study not having the power to demonstrate an effect. These limited data were not analyzed for dose response by the study authors. Nevertheless, this non-positive finding cannot be interpreted as evidence for lack of an effect of the NDMA in ranitidine on bladder cancer, and does not detract from my earlier conclusions.

Wang et al. report an increase in overall cases of esophageal cancer (101 vs. 82 in controls). This did not achieve statistical significance (HR = 1.27, 95% CI 0.95- 1.70, p = 0. 107), possibly

due to the relatively small number of cases observed at this site in Wang's cohort. The authors did not attempt to calculate a dose response relationship for this endpoint. Although these limited findings on esophageal cancer are not definitive in isolation, they are supportive of the finding in my Report that based on the Bradford Hill principles ranitidine use is associated with esophageal cancer, based on associations and dose response observed in epidemiological studies of ranitidine use, and in dietary and occupational studies of NDMA exposure.

EXHIBIT E

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE)
PRODUCTS LIABILITY LITIGATION

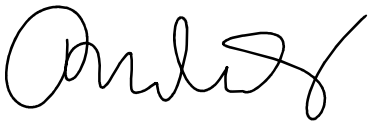
THIS DOCUMENT RELATES TO ALL CASES

MDL NO. 2924

20-MD-2924

RULE 26 SUPPLEMENTAL REPORT OF PAUL J. MICHAELS, M.D.

Paul J. Michaels, M.D.



Date: October 3, 2022

I have reviewed the recent article by Wang and colleagues, published on September 30 in the *International Journal of Environmental Research and Public Health* entitled, "Pharmacoepidemiological research on N-nitrosodimethylamine-contaminated ranitidine use and long-term cancer risk: A population-based longitudinal cohort study."[1] This supplemental report is being issued in order to address the authors' newly-reported findings and interpret these results in the context of my previously written report and deposition testimony. The summary of each study in my original report did not elaborate on all of the nuances, partly because my ultimate synthesis of all the available evidence incorporated further analysis. Within this supplemental report, I describe the study by Wang et al in a greater level of detail to emphasize the strengths of this study and explain how it would affect my full analysis.

Within this article, Wang et al have reported on a very large population-based cohort study of over 55,000 ranitidine users in Taiwan. To gather their subjects and data, the authors used a population-based claims database and a cross-sectional survey participated in by over 99% of Taiwan's population. A large strength of the study was a follow-up of 18 years, particularly important when a cancer diagnosis end-result is being evaluated, with a mean follow-up of between 9 and 10 years for both the ranitidine-treated and untreated cohort groups. Exclusion criteria included patients under 40 years of age, those diagnosed with cancer prior to the index date (date of first prescription of ranitidine), individual prescribed ranitidine for less than 3-months, and those with less than 1-year of follow-up. Focusing on patients older than 40 years of age is a strength, as the cancers evaluated in this study would be unusual in younger individuals. In addition, as a randomized controlled trial using a drug known to contain a carcinogen (NDMA) would be unethical, the researchers in this study further evaluated this population cohort using a 1:1 propensity-score-matching procedure in order to match the large number of ranitidine-treated patients with ranitidine-untreated, famotidine-treated, and proton pump inhibitor (PPI)-treated controls for a longitudinal study, with the latter two comparisons representing an active comparator study to address possible indication bias. Propensity-score-matching allowed the authors to match the cohorts based on age, sex, Charlson Comorbidity Index (CCI), other comorbidities (including hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, and chronic renal disease), medications in addition to famotidine and PPIs, and index date. As mentioned, subjects with less than a 3-month history of ranitidine exposure were excluded from analysis. Further, to assess for a dose response, the authors separated treated subjects based on the number of defined daily doses (DDD), with 90 DDDs representing a 3-month exposure, into four intervals according to the cumulative dose, including 90-180 DDDs, 181-270 DDDs, 271-360 DDDs, and >360 DDDs.

Using a multivariable Cox regression analysis, the authors found that patients treated with ranitidine showed a statistically significant increased risk of various cancers compared to untreated groups, notably including liver cancer (HR: 1.22, 95% CI: 1.09-1.36), gastric cancer (HR: 1.26, 95% CI 1.05-1.52), and pancreatic cancer (HR: 1.35, 95% CI: 1.03-1.77). An increased risk of esophageal cancer (HR: 1.27) and bladder cancer (HR: 1.06) was also seen, though these were not statistically significant (95% CI: 0.95-1.70 and 95% CI: 0.86-1.30, respectively). In addition, with respect to an active comparator analysis, when evaluated in comparison to famotidine users, there was a statistically significant increased risk of all cancers evaluated (HR: 1.07, 95% CI: 1.02-1.12) and liver cancer (HR: 1.22, 95% CI: 1.06-1.40) in the ranitidine-treated cohort. Further, compared to the famotidine-treated group, ranitidine-treated patients also showed an increased risk of esophageal cancer (HR: 1.19, 95% CI: 0.82-1.72), gastric cancer (HR: 1.19, 95% CI: 0.95-1.49), pancreatic cancer (HR: 1.25, 95% CI: 0.90-

[1] Wang CH, Chen II, Chen CH, et al. Pharmacoepidemiological research on N-nitrosodimethylamine-contaminated ranitidine use and long-term cancer risk: A population-based longitudinal cohort study. *Int J Environ Res Public Health* 2022;19:12469.

1.73), and bladder cancer (HR: 1.03, 95% CI: 0.80-1.33), though these increases did not reach statistical significance. Finally, a dose response was seen with ranitidine-treated subjects for liver cancer, where increasing hazard ratios were noted in patients with exposures of 90-180 DDDs (1.03), 181-270 DDDs (1.12), 271-360 (1.26), and over 360 DDDs (1.42), with group exposed to the largest/longest dose >360 DDDs) showing statistical significance (95% CI: 1.22-1.66; $p < 0.001$). Dose-response was also reported for gastric cancer, again with the group exposed to the largest/longest dose >360 DDDs showing statistical significance (95% CI: 1.02-1.74; p=.037). Dose-response was not statistically significant for pancreatic cancer and was not calculated for bladder or esophageal cancer.

A weakness noted from this analysis included the inability to control for certain confounders, including alcohol consumption and cigarette smoking. In addition, the authors were unable to determine patient compliance with ranitidine prescriptions, though it would be unusual for those patients included in the study (subjects with prescriptions >3 months) to have not been relatively compliant with the medication, otherwise additional prescriptions for ranitidine would not have been needed. Also, there was reportedly scarce information with respect to over-the-counter ranitidine use, though it is likely that over-the-counter ranitidine use in the control subjects would have biased the results towards the null, therefore the hazard ratios would have likely been higher if this usage could have been incorporated into the data set. Though dose information was provided using DDDs, it was not tracked for doses exceeding 360 DDD, meaning increases in risk that occur after more than one year of consumption would be diluted.

The defendants have heavily relied on other previously published ranitidine epidemiology studies, particularly various active comparator studies, in order to argue that the known quantities of NDMA within ranitidine are not associated with increased risks of esophageal, gastric, liver, pancreatic, and bladder cancer. However, those studies had significant flaws and weaknesses that are better controlled for in this analysis by Wang and colleagues, allowing for a cleaner data set and an overall stronger study. For example, the study by Iwagami and colleagues[2] which evaluated patients from the Japan Medical Data Center claims database showed a significantly younger population of patients, as the database is only comprised of individuals under the age of 75 years, and the median age of the ranitidine/nizatidine group was only 41.2 years. Whereas, in the study by Wang et al, the mean age for the ranitidine group was 66.8 years and individuals under the age of 40, just approximately 1 year younger than the median age of the Iwagami study, were excluded, given the low incidence of cancer in that age group. Having such a large number of younger individuals in the Iwagami study would heavily bias the results towards the null, as you would not expect many cancer diagnoses regardless of carcinogen exposure in such a young population. In addition, the median follow-up in the Japanese study was only 2.3 years, compared to nearly 4 times that in the current Taiwanese study (median: 8.42 years and mean of 9.56 years for the ranitidine cohort).

Similarly, the nationwide cohort study in South Korea performed by Yoon et al[3] had similar weaknesses to the Iwagami et al study in that the follow-up period was relatively short, restricted to seven years, which the authors themselves discuss as "not long enough to assess the onset of cancer." Another weakness of this study was that there was no comparison to untreated control subjects. Also, although the researchers appeared to stratify individuals by cumulative dosage, date with respect to a dose-response was not reported on in detail. It is also unclear why the study authors felt the need to restrict study participation to those under the age of 80, as examination of those older individuals could have been

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[2] Iwagami M, Kumazawa R, Miyamoto Y, et al. Risk of cancer in association with ranitidine and nizatidine vs other H_2 blockers: Analysis of the Japan medical data center claims database 2005-2018. *Drug Saf* 2021:44:361-71.
[3] Yoon HJ, Kim JH, Seo GH, Park H. Risk of cancer following the use of N-nitrosodimethylamine (NDMA) contaminated ranitidine products: A nationwide cohort study in South Korea. *J Clin Med* 2021;10:1-8.

informative given the increased incidence of malignancy in that portion of the population. The Wang study discusses the Iwagami and Yoon studies, noting on page 12 that its results are more reliable, because "small sample size and short follow-up duration may cause statistical bias and inaccurate conclusions" in the Iwagami and Yoon studies.

Finally, the active comparator analysis published in 2021 by Kim and colleagues[4] did not show a statistically significant increase in cancers of the esophagus, stomach, liver, pancreas, or urinary bladder when comparing ranitidine to either another H2-antagonist (famotidine) or a different, stronger class of acid-blocking medications, proton pump inhibitors (omeprazole). However, there was no comparison made between untreated patients and ranitidine patients. Within this study, adults were defined as being at or above the age of 18. By including such a young population within the study cohort of this analysis, and with incidence of cancer queried for only 10 years, the diagnosis of cancers that are usually restricted to adults over the age of 40-50, and typically much older, would not be identified, therefore limiting the usefulness of this data. In addition, when comparing ranitidine to famotidine, the main active comparator in this analysis, it was determined that patients on famotidine had higher rates of tobacco use, diabetes mellitus, obesity, cirrhosis, inflammatory bowel disease, and atrophic gastritis, conditions that are all associated with higher rates of the various gastrointestinal malignancies being evaluated in this study. These confounding elements, in addition to the young age of the population being studied, also contribute to the profound weaknesses of this study that make it uninformative for the purpose of establishing a carcinogenic effect of ranitidine.

In summary, this study by Wang and colleagues[1] provides additional support and strengthens my opinions that the NDMA in ranitidine can cause cancers in the esophagus, stomach, liver, pancreas, and urinary bladder.

[4] Kim YD, Wang J, Shibli F, et al. No association between chronic use of ranitidine, compared with omeprazole or famotidine, and gastrointestinal malignancies. *Aliment Pharmacol Ther* 2021;54:606-15.

EXHIBIT F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION *THIS DOCUMENT RELATES TO ALL CASES*	MDL NO. 2924 20-MD-2924

SUPPLEMENTAL EXPERT REPORT

JENNIFER LE, PHARMD, MAS, BCPS-ID, FIDSA, FCCP, FCSHP

Date: October 4, 2022 Jennifer Le, Pharm.D., MAS, BCPS-ID, FIDSA, FCCP, FCSHP

Supplemental Report

Jennifer Le, PharmD, MAS, BCPS-ID, FIDSA, FCCP, FCSHP

October 11, 2022

I. Epidemiology

Section VIII, #110 of Le Zantac 2022-0124 Report

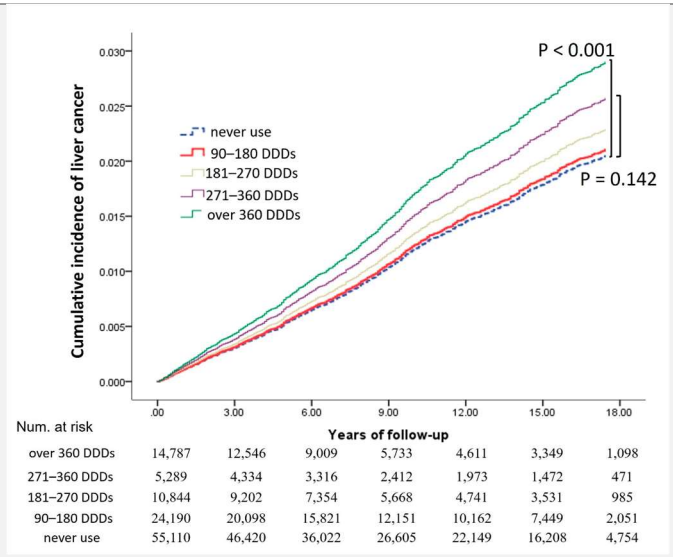
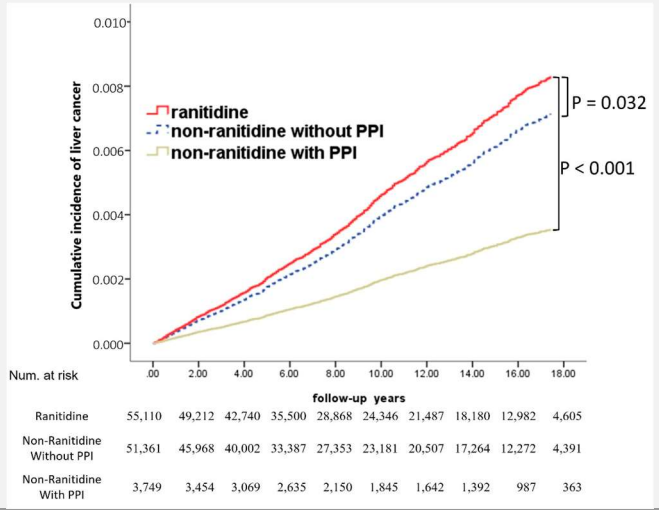
As supplement to this particular section within Epidemiology, I would like to provide my critical evaluation of a recently published article by Wang et al.[1]

The Wang study concluded an association between ranitidine use and liver cancer, gastric cancer and pancreatic cancer. This finding is consistent with multiple other studies that have demonstrated an association between ranitidine use and liver cancer, gastric cancer and pancreatic cancer. This study further bolsters my opinion for liver cancer, gastric cancer and pancreatic cancer that pharmacologic, toxicologic and epidemiologic data of ranitidine and its direct metabolite NDMA all suggest that ranitidine is capable of causing these certain organ-related cancer. The Wang study had elevated, non-statistically significant increased risks for esophageal cancer and non-statistically significant slightly elevated risks for bladder cancer. These findings did not change my opinions regarding bladder and esophageal cancer and my opinion continues to be that the pharmacologic, toxicologic and epidemiologic data of ranitidine and its direct metabolite NDMA all suggest that ranitidine is capable of causing bladder cancer and esophageal cancer.

The following section in the original report was updated to account for all studies:

Of the 15 original research studies reviewed, 7 studies concluded lack of statistical association between ranitidine use and certain types of cancers. Two of these 7 studies evaluated gastric cancer in Asian descent, which suggested potential racial and dietary differences contributing to the results. One meta-analysis suggested that CYP2E1 gene polymorphisms might be a contributing factor against bladder cancer in Asian people.[304] However, these studies should be interpreted cautiously due to the small sample size (noted by the investigators) and they were confounded by the concurrent use of other H2-receptor antagonists (see table for details).

Author Year Study Design and Source of Data	**Ranitidine Dose and Duration**	**Sample Size and Study Period**	**Outcome**	**Comment/Limitation**
Wang 2022[1] Population-based study longitudinal study with propensity score-matching procedure to match the ranitidine-treated group with the ranitidine-untreated group and famotidine controls	Ranitidine at > 90 defined daily dose (i.e, at least 300 mg ranitidine daily for 3 months) Those who never used ranitidine belonged to the non-ranitidine cohort (famotidine with or without proton pump inhibitors)	18 years (January 2000 and December 2018) • 55,110 users of ranitidine • patients were evaluated from the index date until the target cancer onset, death, or the end of the study period	*Based on first-incident of the many cancers. Findings based on Cox regression to allow for control for pertinent co-variates (Figure 2)* Increased risk for all cancer: HR: 1.10, CI: 1.06–1.15, p < 0.001 Increased risk for liver cancer: HR: 1.22, 95% CI: 1.09–1.36, p < 0.001 Increased risk for gastric cancer: HR: 1.26, CI: 1.05–1.52, p = 0.012 Increased risk for pancreatic cancer: HR 1.35, CI: 1.03–1.77, p = 0.030	Large sample size selected from a high-quality nationwide and population-based database with prospective study design, outcome data were retrieved from formal cancer registries and long follow-up period of 18 years Propensity scoring was used to increase the robustness in comparing the groups in allowing control for some pertinent variables. Cox regression adjusted for age, sex, the Charlson comorbidity index, co-medications (aspirin, statins, angiotensin-converting enzyme inhibitors, β-blockers, spironolactone, glucocorticoids, selective serotonin reuptake inhibitors, and antiviral therapy for hepatitis B or C), comorbidities (hypertensive cardiovascular disease, hyperlipidemia, diabetes mellitus, and chronic kidney disease). Authors concluded long-term ranitidine use was associated with a higher likelihood of liver cancer development in ranitidine users compared with the control groups of non-ranitidine users treated with famotidine or proton-pump inhibitors. Evaluated dose-response relationship by 90–180, 181–270, 271–360, and >360 DDDs and indicated significant dose-response relationship over 18 years of study period (see figure) Limitations of study included lack of accurate estimation of NDMA levels and lack of control for alcohol and smoking, and medication compliance was not evaluated.

			Increased risk for lung cancer: HR: 1.17, CI: 1.05–1.31, p = 0.005 No significant associations were observed for the 14 other cancers.	 

II. References

1. Wang, C.-H.; Chen, I.-I.; Chen, C.-H.; Tseng, Y.-T. Pharmacoepidemiological Research on N-Nitrosodimethylamine-Contaminated Ranitidine Use and Long-TermCancer Risk: A Population-Based Longitudinal Cohort Study. Int. J. Environ. Res. Public Health 2022, 19, 12469. https://doi.org/10.3390/ijerph191912469

EXHIBIT G

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA
WEST PALM BEACH DIVISION

CASE NO. 20-md-02924-ROSENBERG

IN RE: ZANTAC (RANITIDINE) PRODUCTS LIABILITY LITIGATION. . West Palm Beach, FL . June 9, 2021 .

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MOTION to MODIFY PTO 30 HEARING (through Zoom)
BEFORE THE HONORABLE ROBIN L. ROSENBERG
UNITED STATES DISTRICT JUDGE and
THE HONORABLE BRUCE REINHART
UNITED STATES MAGISTRATE JUDGE

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expert reports on general causation, even if there is some lingering discovery that is done after that for a few weeks or so. That happens commonly in cases like this, commonly in MDLs. So, I don't think that the deadline for their expert reports to be filed should necessarily correlate with the end of discovery.

I see that -- look, the original PTO 30 had this deadline for generic discovery against Defendants, but also had a final completion of all discovery, including general causation discovery against Defendants. So, it also contemplated that there might be some seepage there, but we had this earlier goal.

So, whether it is written down or not, I think the Plaintiffs right now should be focused on finishing up whatever general causation discovery they need, but it is our kind of strong view, just to differentiate things we don't care about and things we care about, that November 1st should be like the absolute latest that they file their expert reports on general causation.

In cases like this, it is typical that, if something happens later on, somebody moves to supplement.

THE COURT: So, your view, to summarize, is that if December 20th is the general causation deadline for discovery, that an earlier date, such as November 1, a month and 20 days, you know, not quite two months before the end of general