Comparative risk of incidence cancer between histamine-2 receptor antagonists: Preliminary results and lessons from the Feasibility test

Seng Chan You

Background

Popular heartburn drug ranitidine recalled: What you need to know and do

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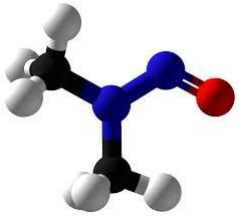
The author of this post has written an update, which you can read here.

If you or a family member take ranitidine (Zantac) to relieve heartburn, you may have heard that the FDA has found a probable human carcinogen (a substance that could cause cancer) in it. The story is unfolding quickly and many details remain murky. Here is what we know so far and what you should do.



- In September 2019, FDA warned about probable carcinogen, N-nitrosodimethylamine (NMDA) in the most famous heartburn medication (ranitidine, *zantac*)
- Subsequently, ranitidine has been voluntarily recalled from the market

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine

Background

- NDMA is classified as a probable human carcinogen (group 2A, a substance that could cause cancer) based on results from laboratory tests

- NDMA is a known environmental contaminant and found in water and foods, including meats, dairy products and vegetables

Background

- It was reported that oral intake of ranitidine increased urinary excretion of NMDA

Zeng et al., Carcinogenesis 2016

- If this low-dose NMDA in ranitidine increases the cancer risk, we need to recommend vigilant cancer screening for ranitidine heavy users.

Background: Valsartan case

FDA updates on voluntary valsartan recalls

The FDA has provided guidance on valsartan recalls that have been occuring recently, providing lists of drugs affected, and methods of impurity testing...

- Valsartan also has been recalled due to presence of NMDA

Background: Valsartan case

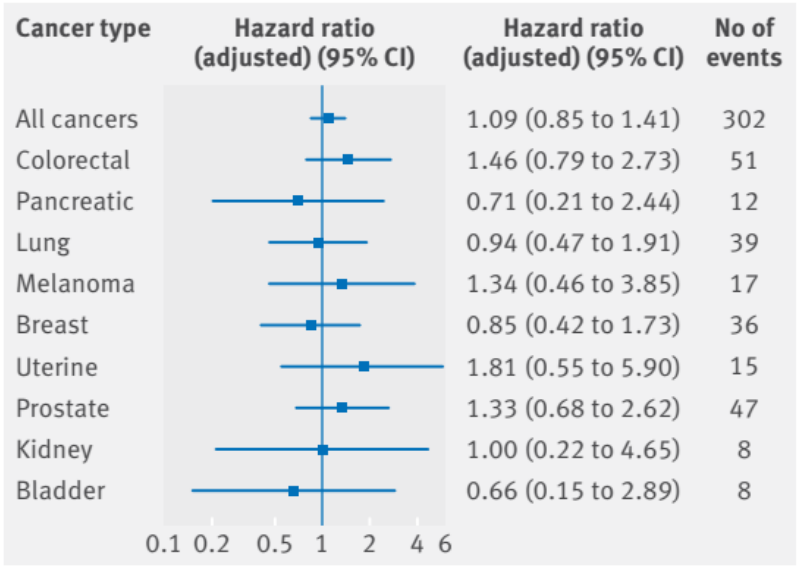


Fig 3 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of single cancer outcomes compared with users of non-contaminated valsartan products. Number of events are total number of events among valsartan users

- In fact, valsartan use was not associated with increased cancer risk in observational study

Pottegård et al., BMJ 2018

Background: Reason for Feasibility test in **distributed observational** research

The likelihood of transforming matter into energy is something akin to shooting birds in the dark in a country where there are only a few birds. Einstein, 1935

Ranitidine is an over-the-counter drug

- To understand how information of OTC drugs have been captured and stored in the OMOP-CDM databases across the various countries and healthcare system
- To understand real-world clinical patterns

https://ohdsi.github.io/TheBookOfOhdsi/ClinicalValidity.html

Method

- Study population (Target and Comparator)
  - Exposure to one of the H2 Receptor Antagonists (H2RAs) of interest longer than 30 days with allowing gaps between the treatment
  - Without use of other H2RAs except the treatment of interest during a previous year
  - Without previous cancer
- List of H2RA
  - Ranitidine, Cimetidine, Nizatidine, Roxatidine, Ramotidine, Lafutidine

Method

- Primary outcome: Overall cancer except thyroid cancer
- Secondary outcomes: Overall cancer, cancer death, and 16 types of cancer
- 99 negative control outcomes
- The hazard ratio of the outcomes for each pairwise comparison of H2RA uses will be estimated

https://github.com/ohdsi-studies/RanitidineCancerRisk

Preliminary result

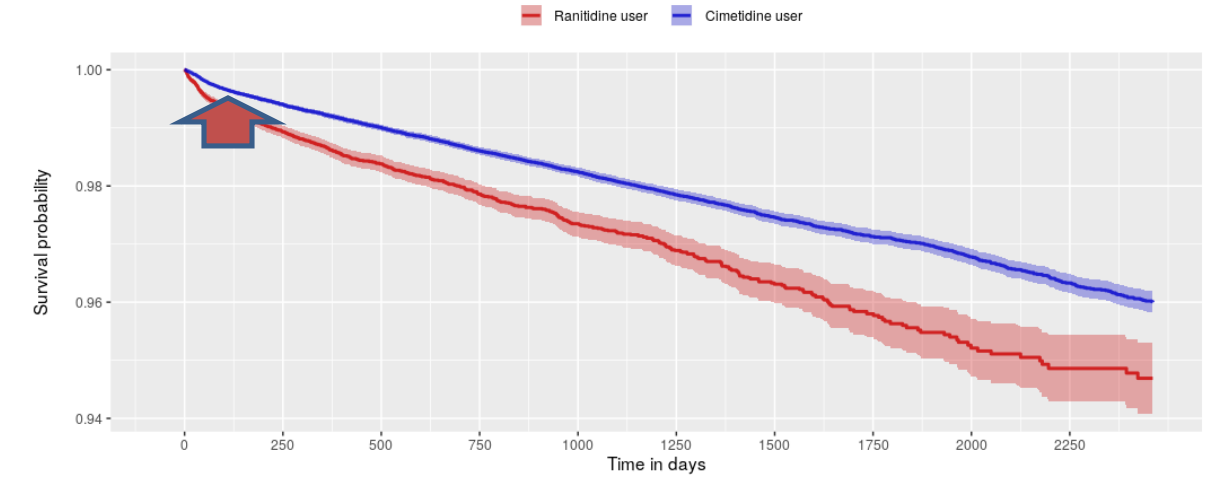
Cohort size, outcome incidence

Database	Target	Comparator	Number of subjects, n		Median follow-up duration, days		Incidence rate, per 1000 PY		MDRR
			T	C	T	C	T	C	
NHIS-NSC	Ranitidine	Cimetidine	34,598	135,155	392	755	8.44	4.57	1.16
		Famotidine	38,574	14,037	377	363	8.50	6.55	1.28
Ajou (EHR)	Ranitidine	Cimetidine	8,564	16,000	622	1,141	6.42	6.47	1.26
		Famotidine	8,968	1,642	625	501	6.17	6.22	1.78
Kangdong (EHR)	Ranitidine	Cimetidine	4,993	1,432	870	858	8.33	3.84	1.68
		Famotidine	5,051	486	870	133	8.47	7.82	2.19
CUMC (EHR)	Ranitidine	Cimetidine	19,113	220	950	1,063	2.45	<6.63	>8.29
		Famotidine	18,461	18,119	956	918	2.52	3.81	1.33

https://data.ohdsi.org/RanitidineCancerRisk/

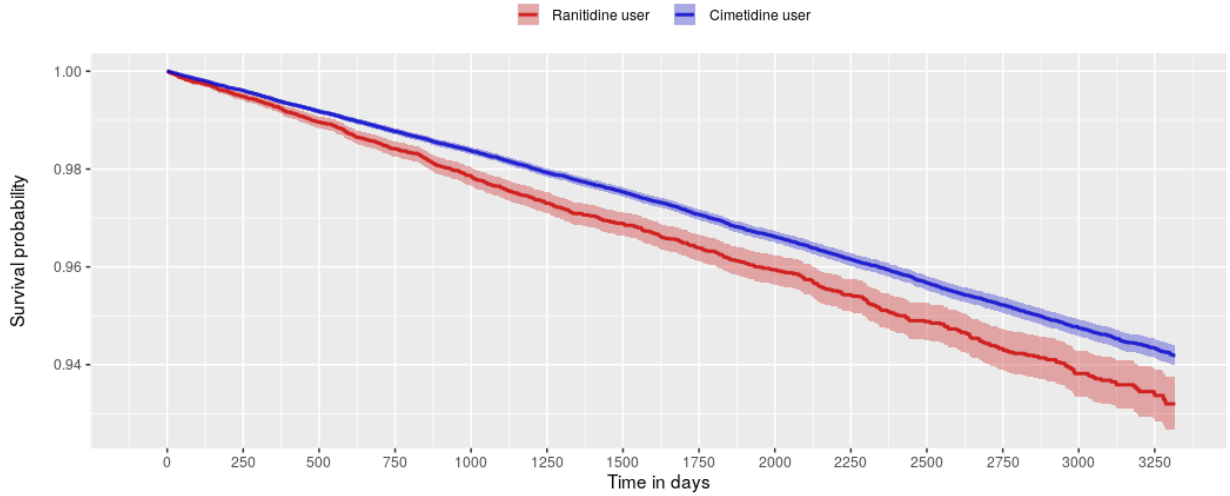
Preliminary result (Survival curve):
Ranitidine vs Cimetidine

ITT



Number at risk										
Ranitidine user	34,768	31,659	22,730	14,650	9,759	6,427	4,339	2,941	2,004	1,360
Cimetidine user	135,303	128,813	107,955	85,147	67,821	53,986	43,043	34,220	26,881	20,603

ITT with 1-year blanking period



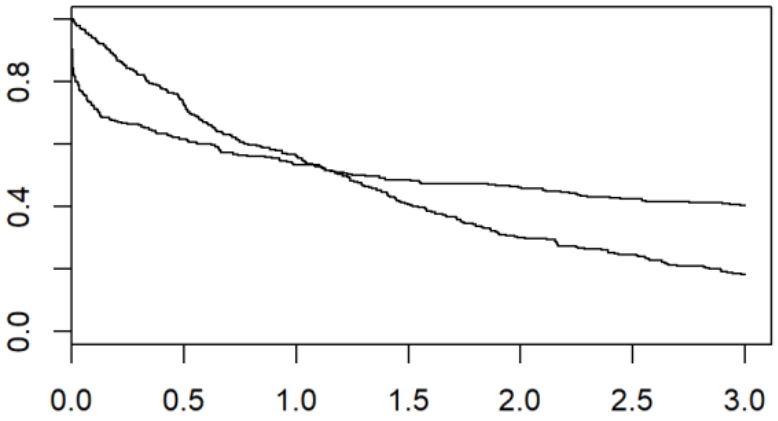
Number at risk														
Ranitidine user	30,043	26,912	23,594	19,986	17,493	14,760	12,497	10,517	8,863	7,335	6,089	4,777	3,570	2,391
Cimetidine user	125,101	117,653	108,660	100,367	93,154	84,770	76,892	68,819	59,309	49,911	42,075	33,255	24,592	16,144

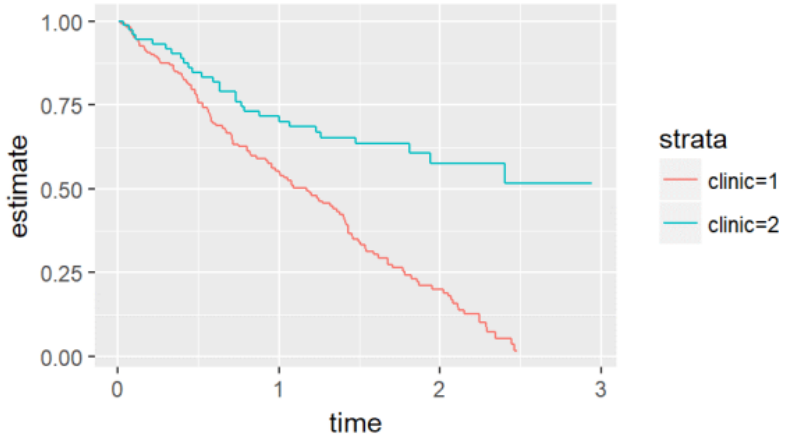
https://data.ohdsi.org/RanitidineCancerRisk/

Violation of the proportional hazards assumption in Cox regression

- Cox proportional hazard model assumes that *ratio* of hazards for any two individuals is **constant** over time.

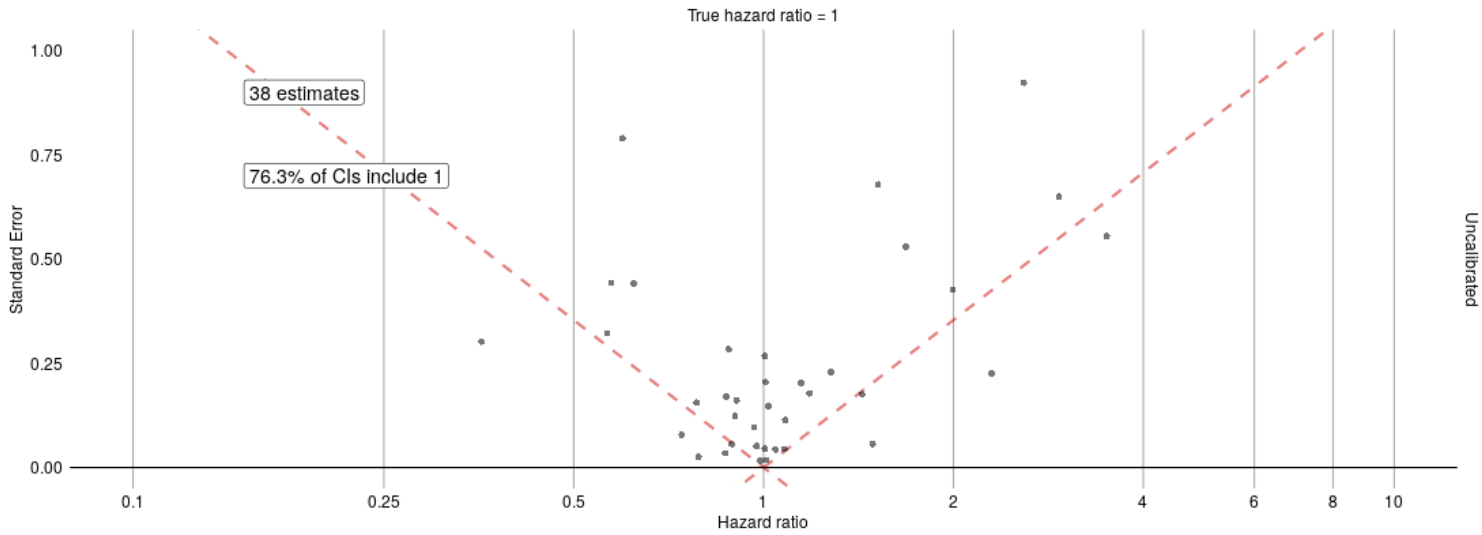
Example of **Non**-proportional hazards



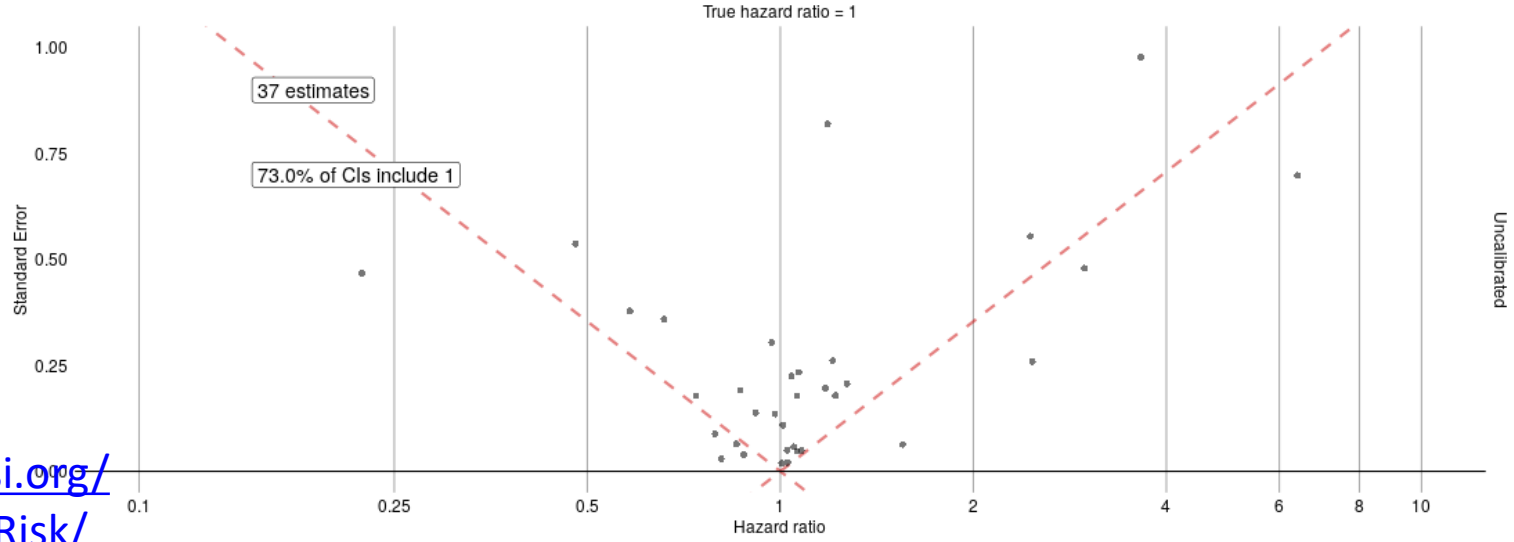


My experience: ranitidine vs cimetidine

ITT



ITT with 1-year blanking period



https://data.ohdsi.org/RanitidineCancerRisk/

Conclusion

- Feasibility test can
  - Validate the cohort definition
    - Previous outcome cohort definitions did not work against EHR data of Ajou university hospital ➔ We revised cohort definition
    - Estimate unadjusted outcome incidence and MDRR
    - Estimate how many negative control outcomes are usable (only one third)
  - Assess the real-world clinical pattern
    - The duration of drug continuation is much longer than I expected
    - The medication patterns was different between US and Korea
  - Assess the feasibility of overall study design
    - It seems feasible to investigate evidence for this OTC drug
  - Identify the violation of proportional hazards assumption
- It is easy to implement of feasibility test in current OHDSI ecosystem
- I recommend to implement feasibility test step in all future OHDSI PLE studies

Join the study!

Comparative risk of the incident cancer between histamine-2 receptor antagonists

Researchers

SCYou Seng Chan You 4d

Dear all,

The new network study is launched to compare the risk of incident cancer between histamine-2 receptor antagonists.

Comparative risk of the incident cancer between histamine-2 receptor antagonists

> **Abstract**: Dietary N-nitrosodimethylamine (NDMA) has been shown to be carcinogenic in animals, however, evidence from population-based studies is inconlusive. The U.S. Food and Drug Administration has issued a statement on ranitidine because they may contain unacceptable levels of NDMA in 2019. To date, there have been several studies regarding association between NDMA exposure and risk of cancer, however, real-world evidence of cancer risk in relation with ranitidine is scarce. We aim to evaluate the comparative risk of incident cancer in patients exposed to various H2 receptor antagonists (H2RAs). We will conduct systematic, multinational study to estimate the relative risk of primary outcome (overall cancer except thyroid cancer) and secondary outcomes (overall cancer, 16 types of cancer, and cancer mortality) in ranitidine cohort. We will compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model after propensity score adjustment.

The package for feasibility test is available at the OHDSI-Studies Repo 2

You can see the more detailed protocol here 3.

Currently, We are searching for collaborators to join this network study and to execute **feasibility test** of this study. Please follow the instruction 2, and please send me the result from the feasibility test first before running `execute` function).

https://github.com/ohdsi-studies/RanitidineCancerRisk


Thank You
for your time