Comparative risk of incidence cancer between histamine-2 receptor antagonists: Preliminary results

Seng Chan You

Background

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

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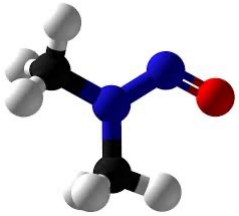
The author of this post has written an update, which you can read here.

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
- 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

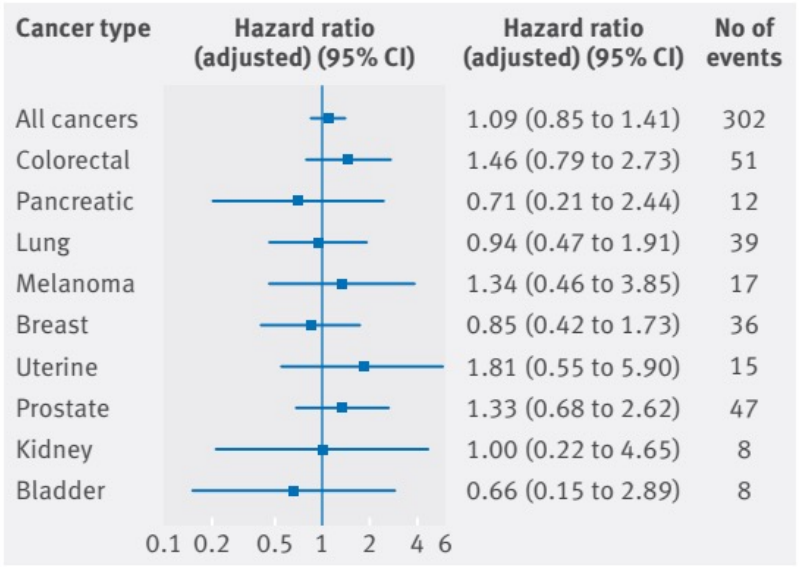


Fig 3 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of single cancer outcomes compared with users of non-contaminated valsartan products. Number of events are total number of events among valsartan users

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

Pottegård et al., BMJ 2018

Method

- Study population
  - Exposure to one of the H_2 Receptor Antagonists (H_2RAs) of interest longer than 30 days with allowing gaps between the treatment
  - Without use of other H_2RAs except the treatment of interest during a previous year
  - Without previous cancer
- Target group: Ranitidine user
- Comparator group : Other H_2RA
  - Nizatidine, Roxatidine, Famotidine, Lafutidine
  - Cimetidine user was excluded from the comparator group since feasibility study shows no empirical equipoise between ranitidine and cimetidine users.

Method

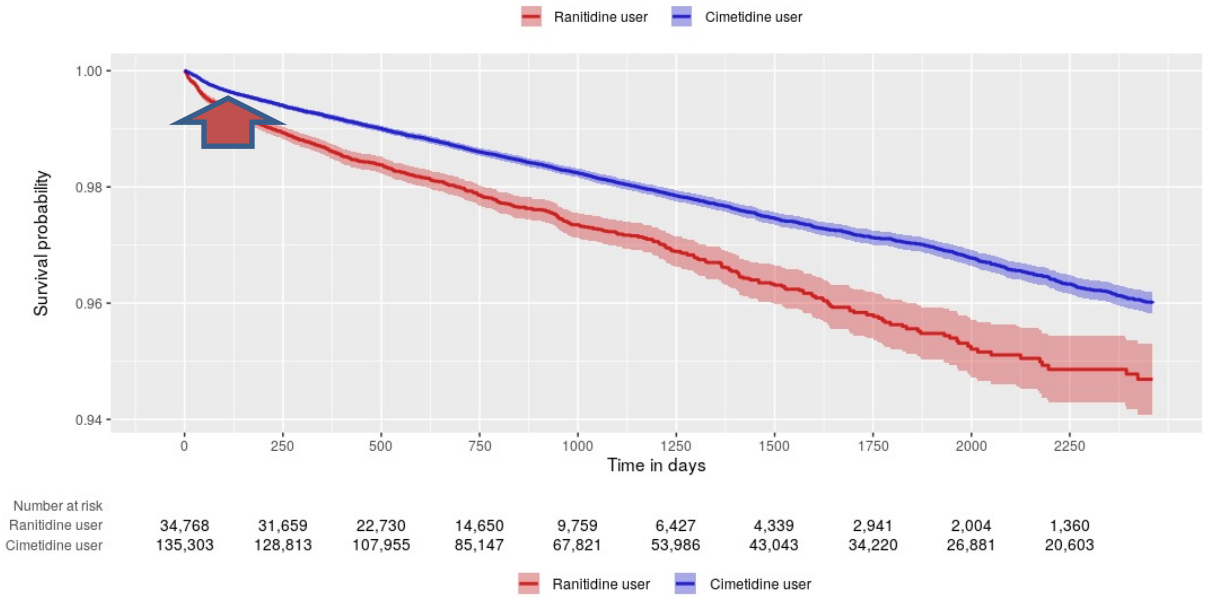
- Primary outcome: Overall cancer except non-melanoma skin cancer
- Secondary outcomes: Overall cancer, cancer death, and 16 types of cancer
- 119 negative control outcomes
- The hazard ratio of the outcomes between ranitidine versus other H_2RA users will be estimated

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

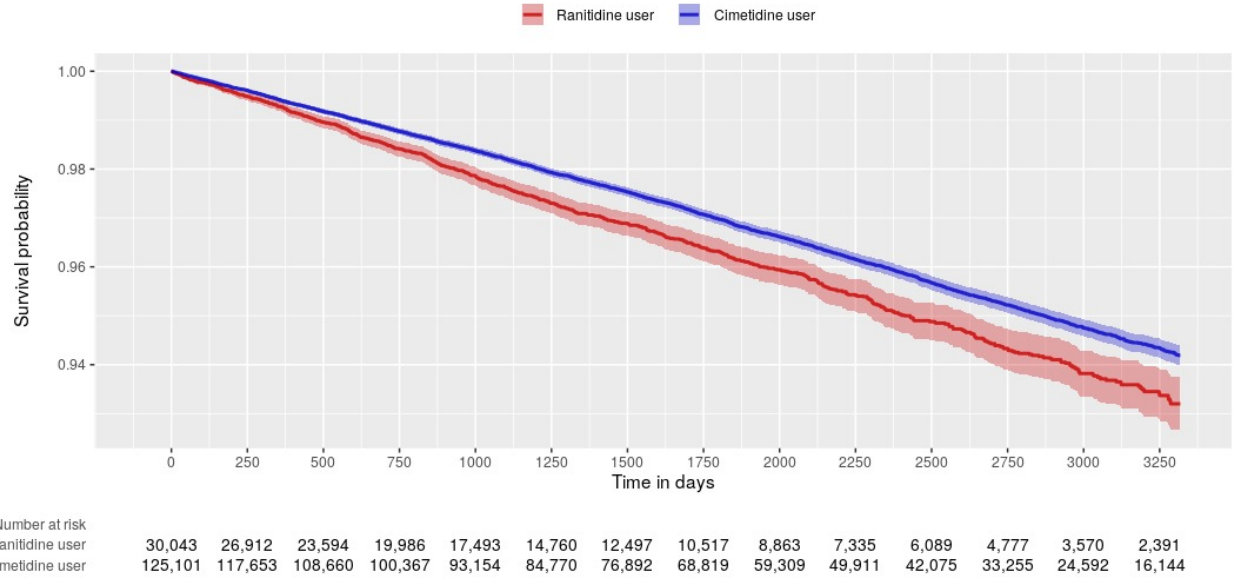
The result from the feasibility test

Ranitidine vs Cimetidine

ITT



ITT with 1-year blanking period



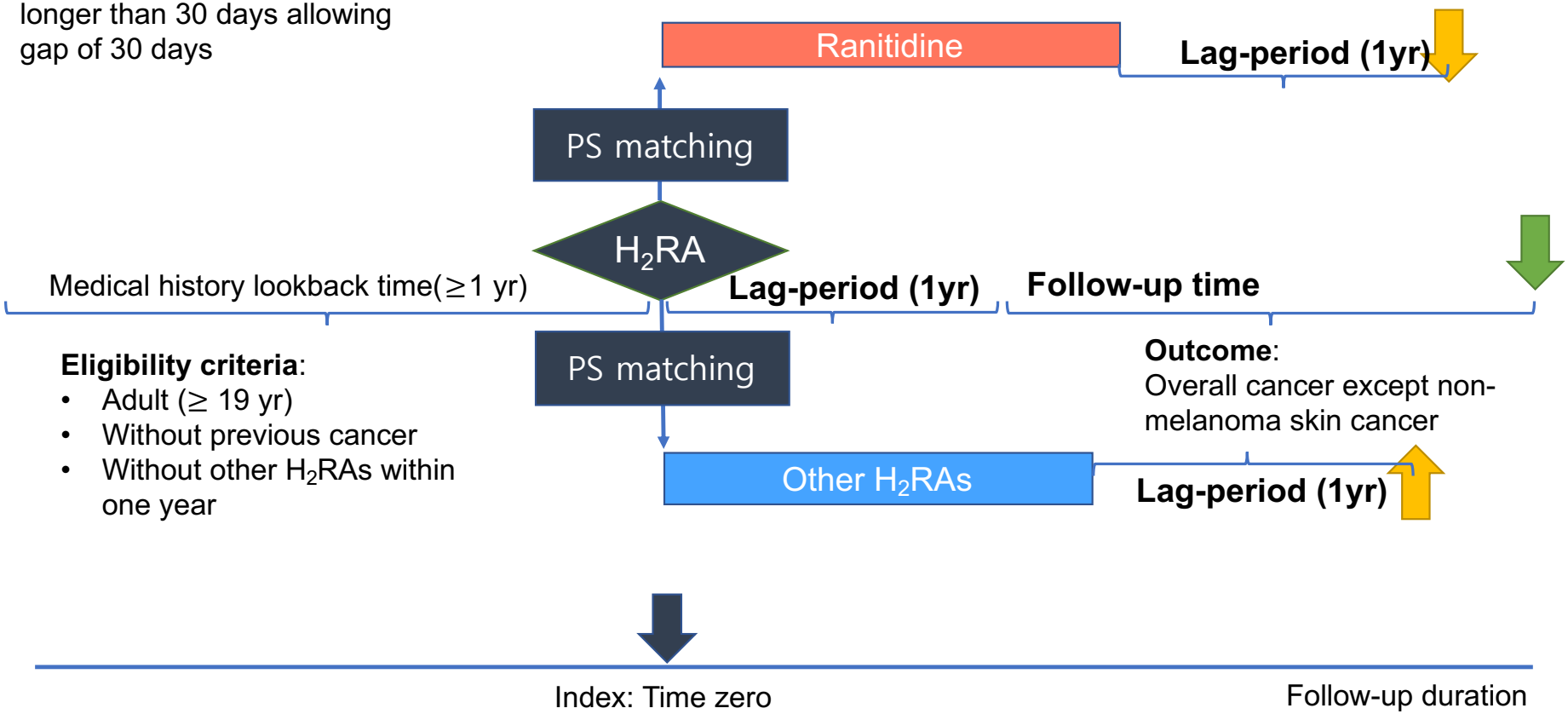
https://data.ohdsi.org/RanitidineCancerRisk/

Primary time-at-risk: ITT with 1-year lag period

Treatment strategies:
- **Ranitidine**
- **Other H_2RAs**

Should be prescribed or longer than 30 days allowing gap of 30 days

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect



Eligibility criteria:
- Adult (≥ 19 yr)
- Without previous cancer
- Without other H_2RAs within one year

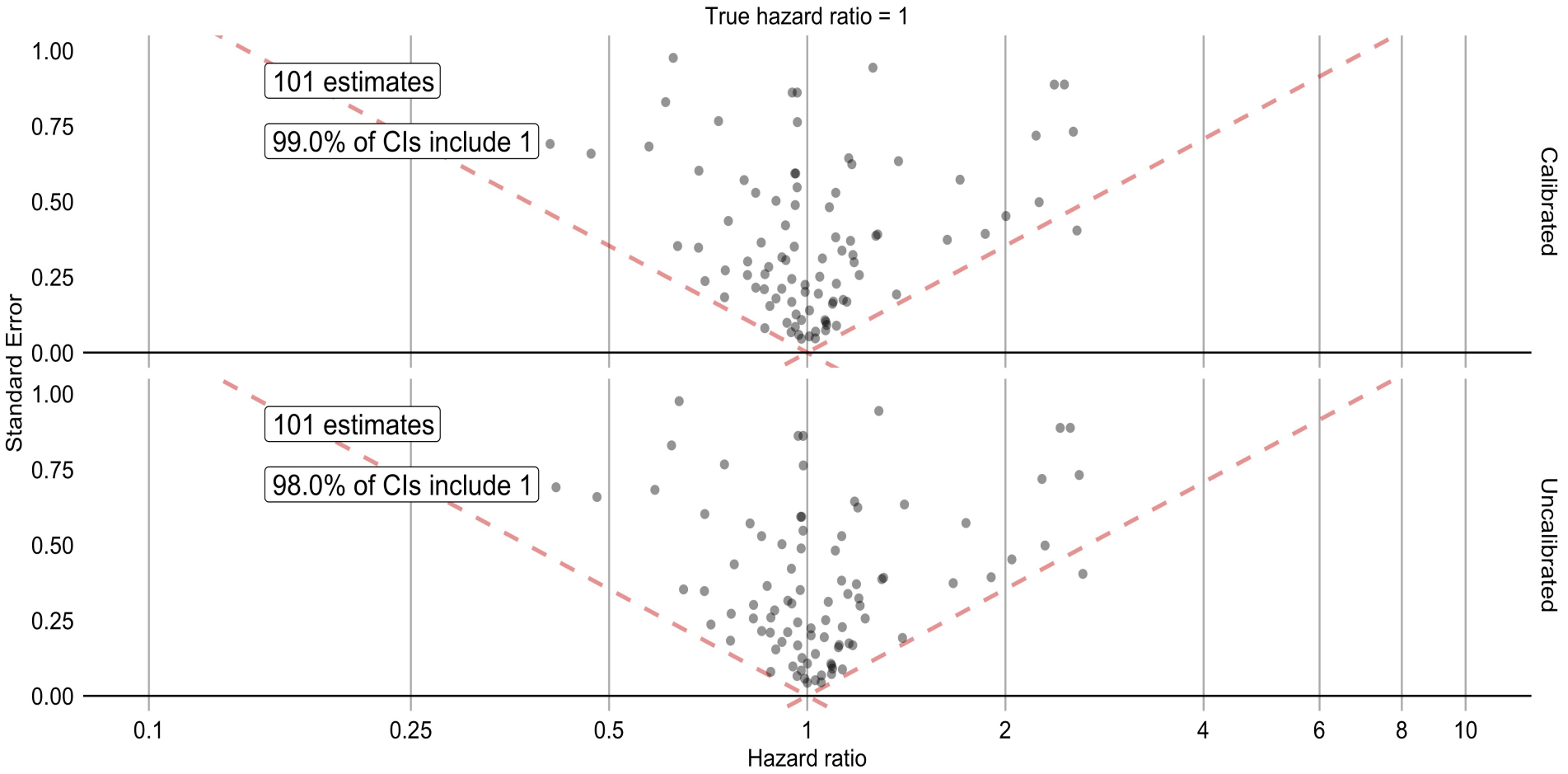
Outcome:
Overall cancer except non-melanoma skin cancer

Preliminary result

Cohort size, outcome incidence

Databases	Number of subjects, n		Mean follow-up duration, year		Incidence rate, per 1000 PY		MDRR
	Ranitidine	Others	Ranitidine	Others	Ranitidine	Others	
AUSOM	9,083	4,838	5.76	6.96	9.40	9.33	1.23
KDH	3,942	3,628	5.49	3.19	9.89	9.24	1.37
NHIS-NSC	30,400	13,525	3.74	4.60	22.66	20.39	1.10
CUIMC	16,717	17,909	3.85	3.67	17.21	15.23	1.13
STARR-OMOP	6,388	9,649	3.34	3.00	13.11	15.32	1.24
Aggregation	66,530	49,549	4.11	4.08	17.08	15.50	1.07

Systematic bias measured by negative control outcomes



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