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

**Version:** 0.5.1

**Authors:**

Seng Chan You, MD, Ajou University, Korea

Seung In Seo, MD, Kangdong Sacred Heart Hospital, Korea

Chan Hyuk Park, MD, Hanyang University College of Medicine, Korea

Rae Woong Park, MD PhD, Ajou University, Korea

**Date:** January 13, 2021

**Acknowledgement:** The analysis is based in part on work from the Observational Health Sciences and Informatics collaborative. OHDSI (<http://ohdsi.org>) is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics.

Table of contents

[2 List of abbreviations 3](#_Toc61855686)

[3 Abstract 4](#_Toc61855687)

[4 Amendments and Updates 4](#_Toc61855688)

[5 Rationale and Background 5](#_Toc61855689)

[6 Study Objectives 5](#_Toc61855690)

[6.1 Research Questions 5](#_Toc61855691)

[6.2 Objectives 7](#_Toc61855692)

[7 Research methods 7](#_Toc61855693)

[7.1 Study Design 7](#_Toc61855694)

[7.1.1 Overview 7](#_Toc61855695)

[7.2 Study population 7](#_Toc61855696)

[7.2.1 Study population 7](#_Toc61855697)

[7.2.2 Subgroups 8](#_Toc61855698)

[7.3 Outcomes 8](#_Toc61855699)

[7.3.1 Primary outcome: Overall cancer except non-melanoma skin cancer 8](#_Toc61855700)

[7.3.2 Secondary outcome: Overall cancer except thyroid cancer 9](#_Toc61855701)

[7.3.3 Secondary outcome: Overall cancer 10](#_Toc61855702)

[7.3.4 Secondary outcome: Lip, oral cavity and pharynx cancer 10](#_Toc61855703)

[7.3.5 Secondary outcome: Esophagus cancer 12](#_Toc61855704)

[7.3.6 Secondary outcome: Stomach cancer 12](#_Toc61855705)

[7.3.7 Secondary outcome: Colon and rectum cancer 13](#_Toc61855706)

[7.3.8 Secondary outcome: Liver cancer 14](#_Toc61855707)

[7.3.9 Secondary outcome: Pancreas cancer 14](#_Toc61855708)

[7.3.10 Secondary outcome: Lung cancer 15](#_Toc61855709)

[7.3.11 Secondary outcome: Breast cancer 16](#_Toc61855710)

[7.3.12 Secondary outcome: Cervix uteri cancer 17](#_Toc61855711)

[7.3.13 Secondary outcome: Corpus uteri cancer 17](#_Toc61855712)

[7.3.14 Secondary outcome: Ovary cancer 18](#_Toc61855713)

[7.3.15 Secondary outcome: Prostate cancer 19](#_Toc61855714)

[7.3.16 Secondary outcome: Bladder cancer 20](#_Toc61855715)

[7.3.17 Secondary outcome: Leukemia 20](#_Toc61855716)

[7.3.18 Secondary outcome: Thyroid cancer 21](#_Toc61855717)

[7.3.19 Secondary outcome: Gall bladder and biliary tract cancer 21](#_Toc61855718)

[7.3.20 Secondary outcome: Additional hospitalization with primary diagnosis of cancer 22](#_Toc61855719)

[7.3.21 Secondary outcome: Cancer mortality 22](#_Toc61855720)

[7.3.22 Negative controls 22](#_Toc61855721)

[7.4 Covariates 26](#_Toc61855722)

[7.4.1 Propensity score covariates 26](#_Toc61855723)

[7.4.2 Other variables 27](#_Toc61855724)

[8 Data Analysis Plan 27](#_Toc61855725)

[8.1 Calculation of time-at-risk 27](#_Toc61855726)

[8.2 Model specification 28](#_Toc61855727)

[8.2.1 Statistical models 28](#_Toc61855728)

[8.2.2 Pooling effect estimates across databases 29](#_Toc61855729)

[8.3 Analyses to perform 29](#_Toc61855730)

[8.4 Output 30](#_Toc61855731)

[8.5 Evidence Evaluation 30](#_Toc61855732)

[8.6 Data Sources 31](#_Toc61855733)

[8.7 Quality control 31](#_Toc61855734)

[8.8 Strengths and Limitations of the Research Methods 32](#_Toc61855735)

[9 Protection of Human Subjects 32](#_Toc61855736)

[10 Plans for Disseminating and Communicating Study Results 32](#_Toc61855737)

[11 References 32](#_Toc61855738)

[12 Appendix: Concept Set Definitions 36](#_Toc61855739)

# List of abbreviations

NMDA N-nitrosodimethylamine

H2RA H2-receptor antagonist

FDA Food and Drug Administration

OHDSI Observational Health Data Sciences and Informatics

PS propensity score

# 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 non-melanoma skin cancer) and secondary outcomes (overall cancer, overall cancer except thyroid 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.

# Amendments and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| 0.1 | February 28 2020 | SC You | Initial draft for feasibility test |
| 0.2 | May 24 2020 | SC You | According to the review from SIDIAP scientific committee, we revised the primary outcome to malignant cancer except non-melanoma skin cancer.  Empirical equipoise will be identified to assess the feasibility of the research |
| 0.3 | July 3 2020 | SC You | We found that cimetidine users are not in equipoise with ranitidine user. So we decided to exclude cimetidine from the other H2 blockers in the primary analysis as comparator of ranitidine users.  We added details for the meta-analysis and diagnostics. |
| 0.4 | October 26 2020 | SC You | We added more negative control outcomes, since we could not identify many negative control outcomes in Korean databases from the feasibility test. |
| 0.5 | January 13, 2021 | SC You | We made following changes:  -Limiting study population to adult  -Primary outcome does not require hospitalization because this information is not available in many databases including UK CPRD. Rather, cancer diagnosis precipitating hospitalization remains as secondary outcomes for sensitivity analysis.  -The criteria for concomitant use of bismuth and sucralfate was changed to avoid immortal time bias.  -Redundant time-at-risk (TAR) settings were removed. Updated protocol will use only four TARs. |
| 0.5.1 | April 20, 2021 | SC You | The study design itself is not changed. The manuscript of protocol is improved based on the pre-specified study design. |

# Rationale and Background

Ranitidine is a histamine H2-receptor antagonist (H2RAs) commonly have been used to treat gastroesophageal reflux disease and peptic ulcer disease and it was top over-the-counter H2RA brand in the USA in 2013. Recent study confirmed that oral intake of ranitidine increases urinary execretion of N-nitrosodimethylamine (NDMA) by nitrosation of ranitidine under stomach-relevant pH conditions in vitro, and the potential cancer risk from ranitidine was suggested.1

In 2019, The US Food and Drug Administration (FDA) has asked doctors and patients to withdraw all ranitidine products from the market as of September 2019, after low levels of the probable human carcinogen NDMA were detected.2 NDMA is known as one of the most potent animal carcinogens and has been shown to be a potent carcinogen across all species that have been investigated.3–7 Hence, the International Agency for Research on Cancer has classified NDMA as “probably carcinogenic to humans” (group 2A).

To date, there have been several studies regarding association between NDMA exposure and risk of cancer,5,8–12 however, real-world evidence of cancer risk in relation with ranitidine is scarce. Recent Danish nationwide cohort study assessed the potential cancer risk associated with NDMA exposure in contaminated valsartan, however, they found no evidence of overall risk of cancer.5 It means that the real-world evidence could be uncertain.

In this study we will generate population-level estimates for comparative risk of malignancy across various H2RAs. We perform every possible pairwise comparison between H2RA treatments for diverse outcome definition related with malignancy.

# Study Objectives

## Research Questions

In this study, we are interested in incidence of cancer in patients exposed to ranitidine compared with those exposed to other H2RAs. Other H2RAs include roxatidine, famotidine, and lafutidine. Nizatidine was excluded from the primary comparison because it has an issue of impurity similar to ranitidine. Cimetidine was excluded from the primary comparison since it does not have empirical equipoise with ranitidine in the pilot study. Furthermore, we conduct the identical analysis for ranitidine versus every ingredient in table 1 (e.g. comparing ranitidine to cimetidine; comparing ranitidine to famotidine).

|  |  |
| --- | --- |
| Drug | OMOP Concept ID |
| Ranitidine | 961047 |
| Cimetidine | 997276 |
| Nizatidine | 950696 |
| roxatidine | 19011685 |
| Famotidine | 953076 |
| lafutidine | 43009003 |

**Table 1**. List of H2 antagonists considered in this study

For each comparison, we are interested in the comparative effect on each of the outcomes listed in table 2. Among them, the primary endpoint is overall cancer except non-melanoma skin cancer. The other secondary outcomes are investigated exploratorily.

|  |  |  |
| --- | --- | --- |
| Outcome | ICD-9-CM | ICD-10 |
| Overall cancer except non-melanoma skin cancer |  |  |
| Overall cancer except thyroid cancer |  |  |
| Overall cancer |  |  |
| Lip, oral cavity and pharynx cancer | 140-149; 160-16113 | C00-C1414 |
| Esophagus cancer | 15015 | C1514 |
| Stomach cancer | 15115 | C1614 |
| Colon and rectum cancer | 153.x; 154.0-154.1, 154.816 | C18-C2114 |
| Liver cancer | 15517,18 | C2214 |
| Pancreas cancer | 15719 | C2514 |
| Lung cancer | 162.x16,20 | C33-C3414 |
| Breast cancer | 174.x16,20 | C5014 |
| Cervix uteri cancer | 18020 | C5314 |
| Corpus uteri cancer | 18221 | C5414 |
| Ovary cancer | 18322 | C5614 |
| Prostate cancer | 18520 | C6114 23 |
| Bladder cancer | 18824 | C6714 |
| Leukemia | 204-20525 | C91-C9514 |
| Thyroid cancer | 19326 | C7323 |
| Gall bladder and biliary tract cancer | 15619 | C23-C2423 |
| Cancer mortality |  |  |

**Table 2**. Outcomes of interest. Supporting references are cited for each outcome.

Primary research question

* Is there any significant difference in incidence of cancers except non-melanoma skin cancer between users of ranitidine and other H2RAs?

The other comparisons except primary research question will be conducted as exploratory investigation.

# Research methods

## Study Design

### Overview

This study will be a retrospective, observational cohort study. By ‘retrospective’ we mean the study will use data already collected at the start of the study. By ‘observational’ we mean no intervention will take place in the course of this study. By ‘cohort study’ we mean two cohorts, a treatment and comparator cohort, will be followed from index date (start of first exposure) to some end date, and assessed for the occurrence of the outcomes of interest. Proportional hazard models will be used to assess the hazard ratios between the two exposure cohorts. Adjustment for baseline confounders will be done using propensity scores.

## Study population

The target group is patients who initiated ranitidine and satisfy criteria below. The primary comparator group is patients who initiated other H2RAs (roxatidine, famotidine, and lafutidine) and satisfy criteria below. Secondary comparator group is patients who initiated any ingredient of H2RAs (cimetidine, nizatidine, roxatidine, famotidine, and lafutidine) and satisfy criteria below.

### Inclusion criteria

All subjects in the database will be included who meet the following criteria: (note: the index date is the start of the treatment of H2RAs)

* Exposure to one of the treatments of interest longer than 30 days with allowing gaps between the treatment
* At least 365 days of observation time prior to the index date
* Without use of other H2RAs except the treatment of interest during a previous year
* Without use of sucralfate or bismuth from 30 days before to 0 days after the index date
* No diagnosis of cancer preceding the index date

The end of on-treatment duration is defined as the end of the exposure of the drug of interest, allowing for 30-day gaps between consecutive prescriptions or start of H2RAs other than the drug of interest.

### Subgroups

Interaction effects will be estimates with the following subgroups:

* Female
* Elderly (age >=65)
* Users with cumulative drug dose more than 365 units
* Users with cumulative drug dose more than 730 units
* Users with cumulative drug dose more than 1095 units

**Gender = female**

Defined as having gender = female (concept ID 8532).

**Elderly (age >=65)**

Defined as having index year – year of birth >= 65.

**Users with cumulative drug dose more than 365 units**

Defined as cumulative quantity of the H2RAs more than 365 during on-treatment period.

**Users with cumulative drug dose more than 730 units**

Defined as cumulative quantity of the H2RAs more than 730 during on-treatment period.

**Users with cumulative drug dose more than 1095 units**

Defined as cumulative quantity of the H2RAs more than 1095 during on-treatment period.

## Outcomes

### Primary outcome: Overall cancer except non-melanoma skin cancer

Index rule defining the index date:

* Occurrence of malignant neoplasm except non-melanoma skin cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date

Appendix 1: Concept Set Definitions

1. Malignant neoplasm except non-melanoma skin cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |
| 4111921 | Squamous cell carcinoma of skin | Condition | SNOMED | YES | YES | NO |
| 4112752 | Basal cell carcinoma of skin | Condition | SNOMED | YES | NO | NO |

### Secondary outcome: Overall cancer except thyroid cancer

Index rule defining the index date:

* Occurrence of malignant neoplasm except thyroid cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for the malignant neoplasm except thyroid cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Malignant neoplasm except thyroid cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |
| 4178976 | Malignant tumor of thyroid gland | Condition | SNOMED | YES | YES | NO |
| 4201622 | Metastasis from malignant tumor of thyroid | Condition | SNOMED | YES | NO | NO |
| 36717298 | Secondary malignant neoplasm of lymph nodes of neck from thyroid | Condition | SNOMED | YES | NO | NO |

### Secondary outcome: Overall cancer

Index rule defining the index date:

* Occurrence of malignant neoplasm for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for the malignant neoplasm as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Malignant neoplasm

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Lip, oral cavity and pharynx cancer

Index rule defining the index date:

* Occurrence of lip, oral cavity and pharynx cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for the lip, oral cavity and pharynx cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Lip, oral cavity and pharynx cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 22557 | Malignant tumor of submandibular gland | Condition | SNOMED | NO | NO | NO |
| 22839 | Overlapping malignant neoplasm of larynx | Condition | SNOMED | NO | NO | NO |
| 25189 | Malignant tumor of oral cavity | Condition | SNOMED | NO | NO | NO |
| 26052 | Primary malignant neoplasm of larynx | Condition | SNOMED | NO | NO | NO |
| 28083 | Primary malignant neoplasm of pharynx | Condition | SNOMED | NO | NO | NO |
| 28356 | Overlapping malignant neoplasm of major salivary gland | Condition | SNOMED | NO | NO | NO |
| 31509 | Primary malignant neoplasm of tonsil | Condition | SNOMED | NO | NO | NO |
| 132258 | Primary malignant neoplasm of frontal sinus | Condition | SNOMED | NO | NO | NO |
| 132565 | Primary malignant neoplasm of vermilion border of lower lip | Condition | SNOMED | NO | NO | NO |
| 132832 | Primary malignant neoplasm of inner aspect of lip | Condition | SNOMED | NO | NO | NO |

### Secondary outcome: Esophagus cancer

Index rule defining the index date:

* Occurrence of esophagus cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for esophagus cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Esophagus cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4181343 | Malignant tumor of esophagus | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Stomach cancer

Index rule defining the index date:

* Occurrence of stomach cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for stomach cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Stomach Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443387 | Malignant tumor of stomach | Condition | SNOMED | NO | YES | NO |
| 46271647 | Malignant carcinoid tumor of stomach | Condition | SNOMED | YES | YES | NO |

### Secondary outcome: Colon and rectum cancer

Index rule defining the index date:

* Occurrence of colon cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for colon cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Colon and rectum cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443390 | Malignant tumor of rectum | Condition | SNOMED | NO | YES | NO |
| 443391 | Malignant tumor of cecum | Condition | SNOMED | NO | YES | NO |
| 4180790 | Malignant tumor of colon | Condition | SNOMED | NO | YES | NO |
| 40481907 | Carcinoid tumor | Condition | SNOMED | YES | YES | NO |
| 44501937 | Goblet cell carcinoid of Ascending colon | Condition | ICDO3 | YES | NO | NO |
| 44502103 | Carcinoid tumor of Colon | Condition | ICDO3 | YES | NO | NO |

### Secondary outcome: Liver cancer

Index rule defining the index date:

* Occurrence of liver cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for liver cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Liver Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 198700 | Secondary malignant neoplasm of liver | Condition | SNOMED | YES | YES | NO |
| 4246127 | Malignant neoplasm of liver | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Pancreas cancer

Index rule defining the index date:

* Occurrence of liver cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for liver cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Pancreas Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4178966 | Malignant tumor of ampulla of Vater | Condition | SNOMED | YES | YES | NO |
| 4180793 | Malignant tumor of pancreas | Condition | SNOMED | NO | YES | NO |

Showing 1 to 2 of 2 entries

Previous1Next

### Secondary outcome: Lung cancer

Index rule defining the index date:

* Occurrence of lung cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for lung cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Lung Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 254583 | Kaposi's sarcoma of lung | Condition | SNOMED | YES | YES | NO |
| 254591 | Secondary malignant neoplasm of lung | Condition | SNOMED | YES | YES | NO |
| 443388 | Malignant tumor of lung | Condition | SNOMED | NO | YES | NO |
| 4157333 | Malignant neoplasm of main bronchus | Condition | SNOMED | NO | YES | NO |
| 4177112 | Malignant tumor of trachea | Condition | SNOMED | NO | YES | NO |
| 4311499 | Primary malignant neoplasm of respiratory tract | Condition | SNOMED | NO | NO | NO |

### Secondary outcome: Breast cancer

Index rule defining the index date:

* Occurrence of breast cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for breast cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Breast cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 135489 | Primary malignant neoplasm of male breast | Condition | SNOMED | YES | YES | NO |
| 140960 | Secondary malignant neoplasm of female breast | Condition | SNOMED | YES | YES | NO |
| 442178 | Secondary malignant neoplasm of male breast | Condition | SNOMED | YES | YES | NO |
| 4112853 | Malignant tumor of breast | Condition | SNOMED | NO | YES | NO |
| 4157448 | Carcinoma of male breast | Condition | SNOMED | YES | YES | NO |
| 4244051 | Malignant melanoma of skin of breast | Condition | SNOMED | YES | YES | NO |
| 4247348 | Primary malignant neoplasm of skin of breast | Condition | SNOMED | YES | YES | NO |
| 4313931 | Secondary malignant neoplasm of skin of breast | Condition | SNOMED | YES | YES | NO |

### Secondary outcome: Cervix uteri cancer

Index rule defining the index date:

* Occurrence of cervix uteri cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for cervix uteri cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Cervix uteri cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 198984 | Malignant tumor of cervix | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Corpus uteri cancer

Index rule defining the index date:

* Occurrence of corpus uteri cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for corpus uteri cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Corpus uteri cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 197230 | Malignant neoplasm of uterus | Condition | SNOMED | NO | YES | NO |
| 198984 | Malignant tumor of cervix | Condition | SNOMED | YES | YES | NO |
| 4048225 | Neoplasm of endometrium | Condition | SNOMED | NO | YES | NO |
| 4241777 | Carcinoma in situ of endometrium | Condition | SNOMED | YES | YES | NO |
| 4303970 | Endometrial intraepithelial neoplasia | Condition | SNOMED | YES | NO | NO |

### Secondary outcome: Ovary cancer

Index rule defining the index date:

* Occurrence of ovary cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for ovary cancer as a primary diagnosis on or after the index date
* Only female gender

Appendix 1: Concept Set Definitions

1. Ovary Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 199752 | Secondary malignant neoplasm of ovary | Condition | SNOMED | YES | YES | NO |
| 200052 | Primary malignant neoplasm of uterine adnexa | Condition | SNOMED | NO | YES | NO |
| 4181351 | Malignant tumor of ovary | Condition | SNOMED | NO | YES | NO |
| 4312824 | Secondary malignant neoplasm of broad ligament | Condition | SNOMED | YES | YES | NO |
| 40486213 | Malignant neoplasm of broad ligament of uterus | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Prostate cancer

Index rule defining the index date:

* Occurrence of prostate cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for prostate cancer as a primary diagnosis on or after the index date
* Only male gender

Appendix 1: Concept Set Definitions

1. Prostate cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4163261 | Malignant tumor of prostate | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Bladder cancer

Index rule defining the index date:

* Occurrence of bladder cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for bladder cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Bladder cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 197508 | Malignant tumor of urinary bladder | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Leukemia

Index rule defining the index date:

* Occurrence of leukemia for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for leukemia as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Leukemia

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 133169 | Myelofibrosis | Condition | SNOMED | NO | YES | NO |
| 135214 | Polycythemia vera | Condition | SNOMED | NO | YES | NO |
| 317510 | Leukemia | Condition | SNOMED | NO | YES | NO |
| 4297355 | Aggressive NK-cell leukemia involving skin | Condition | SNOMED | NO | YES | NO |
| 40492268 | Myelodysplastic/myeloproliferative disease | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Thyroid cancer

Index rule defining the index date:

* Occurrence of thyroid cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date
* Hospitalization for thyroid cancer as a primary diagnosis on or after the index date

Appendix 1: Concept Set Definitions

1. Thyroid cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4178976 | Malignant tumor of thyroid gland | Condition | SNOMED | NO | YES | NO |

### Secondary outcome: Gall bladder and biliary tract cancer

Index rule defining the index date:

* Occurrence of gall bladder and biliary tract cancer for the first time in the person’s history

Additional inclusion criteria:

* At least 365 days of observation time prior to the index date

Appendix 1: Concept Set Definitions

1. Gall bladder and biliary tract cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 4181345 | Malignant tumor of biliary tract | Condition | SNOMED | NO | YES | NO |
| 40490929 | Primary malignant neoplasm of intrahepatic bile duct | Condition | SNOMED | YES | YES | NO |

### Secondary outcome: Additional hospitalization with primary diagnosis of cancer

As a sensitivity analysis, stricter outcomes requiring hospitalization with primary diagnosis of cancer for all 19 outcomes above are investigated.

### Secondary outcome: Cancer mortality

Index rule defining the index date:

* A death occurrence from cancer

Appendix 1: Concept Set Definitions

1. Cancer

| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| --- | --- | --- | --- | --- | --- | --- |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

### Negative controls

Negative controls are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Negative controls are selected using a similar process to that outlined by Voss et al27. Once potential negative control candidates were selected, manual clinical review to exclude any pairs that may still be in a causal relationship or similar to the study outcome was be performed to select the top concepts by patient exposure. The final list of 119 negative outcomes is described in Table 3.

|  |  |
| --- | --- |
| **Concept ID** | **Concept Name** |
| 443698 | Abnormal anal Papanicolaou smear |
| 443585 | Abrasion and/or friction burn of multiple sites |
| 380818 | Acquired deformity of head |
| 31668 | Acquired deformity of neck |
| 4319325 | Acquired deformity of trunk |
| 432411 | Acquired equinus deformity of foot |
| 439673 | Acute hepatitis B with delta-agent (coinfection) without hepatic coma |
| 441481 | Adult victim of abuse |
| 4218106 | Alcoholism |
| 4303805 | Allergic reaction to bite and/or sting |
| 4101660 | Amputated below knee |
| 4198962 | Amputated thumb |
| 4171556 | Ankle ulcer |
| 77650 | Aseptic necrosis of bone |
| 439237 | Assault |
| 141797 | Black piedra |
| 79232 | Burn of ankle |
| 4172458 | Candidiasis of skin |
| 42709838 | Cellulitis of lower limb |
| 439674 | Chronic viral hepatitis B without delta-agent |
| 4047787 | Colles' fracture |
| 134734 | Compartment syndrome |
| 72995 | Contracture of joint of hand |
| 80492 | Contracture of knee joint |
| 439666 | Contracture of multiple joints |
| 199978 | Contusion of lower limb |
| 433071 | Contusion of multiple sites |
| 201606 | Crohn's disease |
| 75389 | Current tear of lateral cartilage AND/OR meniscus of knee |
| 80242 | Current tear of medial cartilage AND/OR meniscus of knee |
| 73575 | Deformity of toe |
| 436906 | Disease caused by rickettsiae |
| 4135080 | Dislocation of radial head |
| 78834 | Effusion of joint of hand |
| 4247710 | Effusion of joint of pelvic region |
| 72407 | Effusion of joint of shoulder region |
| 4150043 | Epididymitis |
| 197607 | Excessive and frequent menstruation |
| 374801 | Foreign body in ear |
| 4131595 | Fracture of radius |
| 441487 | Frostbite |
| 40481632 | Ganglion cyst |
| 74855 | Genital herpes simplex |
| 437744 | Heat exhaustion |
| 440021 | Herpes simplex without complication |
| 437489 | Herpes zoster with complication |
| 440329 | Herpes zoster without complication |
| 435511 | Hypercalcemia |
| 77364 | Hypermobility of coccyx |
| 74731 | Hypertrophic osteoarthropathy |
| 440129 | Hypertrophy of nasal turbinates |
| 440072 | Hypogammaglobulinemia |
| 4344500 | Impingement syndrome of shoulder region |
| 434872 | Infection by Trichomonas |
| 440053 | Infestation by insect |
| 4057662 | Infestation by Phthirus |
| 4168222 | Intra-abdominal and pelvic swelling, mass and lump |
| 72994 | Jaccoud's syndrome |
| 78512 | Joint contracture of the ankle and/or foot |
| 78228 | Joint derangement |
| 77072 | Joint effusion of ankle AND/OR foot |
| 72404 | Joint stiffness |
| 435903 | Juvenile osteochondrosis of foot |
| 438527 | Juvenile osteochondrosis of lower extremity, excluding foot |
| 435633 | Juvenile osteochondrosis of upper extremity |
| 4115991 | Knee joint effusion |
| 435516 | Lipoprotein deficiency disorder |
| 4297984 | Local infection of wound |
| 440638 | Lyme disease |
| 438067 | Malaria |
| 438297 | Mechanical complication of cardiac device, implant AND/OR graft |
| 432798 | Mechanical complication of internal orthopedic device, implant AND/OR graft |
| 137967 | Muscle, ligament and fascia disorders |
| 4271024 | Musculoskeletal fibromatosis |
| 4209423 | Nicotine dependence |
| 201792 | Nongonococcal urethritis |
| 72413 | Nontraumatic rupture of muscle |
| 4215978 | Onychomycosis |
| 140648 | Onychomycosis due to dermatophyte |
| 4129408 | Open wound of ankle |
| 4053600 | Open wound of elbow |
| 77139 | Open wound of finger without complication |
| 444426 | Open wound of foot except toes without complication |
| 137426 | Open wound of forearm without complication |
| 77421 | Open wound of hand except fingers without complication |
| 4051004 | Open wound of scalp |
| 4129404 | Open wound of upper arm |
| 438120 | Opioid dependence |
| 4171915 | Orchitis |
| 315361 | Orthopnea |
| 74080 | Orthostatic proteinuria |
| 75920 | Osteitis condensans |
| 437359 | Osteochondritis dissecans |
| 378160 | Otorrhea |
| 77356 | Pathological dislocation of joint |
| 375292 | Perforation of tympanic membrane |
| 253796 | Pneumothorax |
| 4295261 | Postmenopausal state |
| 4094448 | Pregnancy test negative |
| 198715 | Premature menopause |
| 199876 | Prolapse of female genital organs |
| 4295888 | Prolapse of intestine |
| 194997 | Prostatitis |
| 4245252 | Raised prostate specific antigen |
| 4345332 | Spinal instability |
| 4195698 | Tenosynovitis |
| 4339088 | Testicular mass |
| 80946 | Tinea manus |
| 4163280 | Tinea of perianal region |
| 133141 | Tinea pedis |
| 440268 | Toxic effect of carbon monoxide |
| 81930 | Transient arthropathy |
| 74719 | Ulcer of foot |
| 443593 | Ulcer of thigh |
| 4092565 | Uterine prolapse |
| 435131 | Victim of neglect |
| 261599 | Vocal cord paralysis |
| 132834 | White piedra |
| 435723 | Wound seroma |

**Table 3**. Negative control outcomes

## Covariates

### Propensity score covariates

Propensity scores (PS) will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates.

The types of baseline covariates used to fit the propensity score model will be:

* Demographics
  + Gender
  + Age
  + Age group (5-year bands)
  + Index year
  + Race
* Conditions
  + Any time prior
  + In prior 30d
  + In prior 365d
* Condition aggregation
  + SNOMED
* Drugs
  + In prior 30d
  + In prior 365d
  + Overlapping index date
* Drug aggregation
  + Ingredient
  + ATC Class
* Procedure
  + In prior 365d
* Measurement
  + In prior 30d
  + In prior 365d
  + Range Group in prior 365d
* Observation
  + In prior 365d
* Risk scores
  + Charlson comorbidity index
* Visit count
  + In prior 365d

Specific covariates to be excluded from the propensity score model are labelled **concepts to exclude,** which composed of drug use of H2RAs.

All covariates that occur in fewer than 0.1% of the persons between the target and comparator cohorts combined will be excluded prior to model fitting for computational efficiency.

### Other variables

None

# Data Analysis Plan

## Calculation of time-at-risk

Four time-at-risk periods will be used:

* Intent-to-treat: Starting on the day of treatment initiation and stopping at the end of observation.
* Intent-to-treat with one-year lag period: Starting 365 days after the day of treatment initiation and stopping at the end of observation.
* On-treatment: Starting on the day of treatment initiation, and stopping at treatment end or at starting H2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.
* On-treatment with one-year lag period: Starting 365 days after treatment initiation, and stopping 1 year after treatment end or starting H2RAs other than the target drug, allowing for a maximum gap of 30 days between prescriptions.

## Model specification

In this study, we 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. A pre-specified *P*<0.05 was considered statistically significant for all two-sided tests.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window (the cohort start date), until the earliest event among 1) the first occurrence of the outcome, 2) the end of the time-at-risk window, and 3) the end of the observation period that spans the time-at-risk start.

Incidence rates will be computed for each outcome in each exposure group

### Statistical models

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation using 10 replications per fold, a starting variance of 0.01 and a tolerance of 2e-7. Covariates to be used in the propensity score model are listed in section 7.4.1.

* One-to-one PS matching: After estimating the PS, one-to-one matching will be performed. A caliper of 0.2 times the standard deviation of the propensity score distribution, and a greedy matching will be used. The outcome model will be fitted using an unconditioned Cox regression, with only the treatment variable as predictor.
* Variable ratio PS matching: the two cohorts were matched with a maximum ratio of 10. A caliper of 0.2 times the standard deviation of the propensity score distribution, and a greedy matching will be used. The outcome model will be fitted using a stratified Cox regression conditioned on the matched sets, with only the treatment variable as predictor.
* PS stratification: The target cohort and comparator cohorts will be stratified into ten quantiles of the propensity score distribution. The final outcome model will apply a conditional Cox proportional hazard model, conditions on the propensity score strata.
* Without matching: The Cox proportional hazard model will be applied without PS matching or stratification.

If there is any covariate with standardized differences greater than 0.1 between target and comparator cohort after PS adjustment, then the PS adjustment will be considered as sub-optimal or non-balanced. And these results will be considered as results for sensitivity analysis.

Interactions between the treatment effect and the predefined subgroups will be evaluated in separate outcome models, one per subgroup. For efficiency reasons, only one-to-one PS matching will be used when investigating effect interactions

Incidence rates will be computed for each outcome in each exposure group.

### Pooling effect estimates across databases

Random-effects model meta-analysis will be performed to calculate summary hazard ratio for pooling effect estimates across databases.

The only balanced results after PS adjustment will be aggregated to the primary analysis.

## Analyses to perform

The following comparative analyses will be performed:

* 6 comparisons: Pairwise comparison among six H2RA users.
* 39 outcomes: 1 primary outcome + 18 secondary outcomes + 19 narrow outcomes requiring hospitalization with primary diagnosis of cancer + cancer mortality
* 4 time-at-risk definitions
* 4 model: unconditioned Cox regression after 1:1 PS matching, Cox regression without matching, conditioned Cox regression after variable-ratio PS matching, and conditioned Cox regression after PS stratification
* Additional 6 interaction analysis for 20 outcomes

The total number of analyses is 5,184 (6 comparisons x 39 outcomes x 4 TAR x 4 statistical models + 12x6x20 interaction analyses) in each database (**Table 4**).

Among these analyses, the result from meta-analysis using balanced results from the one-to-one PS matching using to-treat time-at-risk with one-year blanking period between ranitidine and cimetidine users regardless of history of gastric ulcer will be reported as the primary outcome.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Target | Comparator | Stratification | Outcomes | Time-at-risk | Statistical model | Subgroup analysis |
| Exposure to the ranitidine | H2 Blocker exposure  -Other H2 blockers (roxatidine, famotidine, and lafutidine)  -Cimetidine  -Nizatidine  -Roxatidine  -Famotidine  -Lafutidine | -Based on previous history of gastric ulcer | Primary outcome:  Overall cancer except non-melanoma skin cancer  Secondary outcome:  - Overall cancer except thyroid cancer  - Overall cancer  - 16 subtypes of cancer  - 19 additional outcomes requiring hospitalization  - Cancer mortality | \*Intent-to-treat  \*Intent-to-treat with one-year lag period  \*On-treatment  \*On-treatment with one-year lag period | \* One-to-one PS matching  \*Variable ratio PS matching  \*PS stratification  \*Without matching | \* Female  \* Elderly (age >=65)  \* Users with cumulative drug dose more than 365 units  \* Users with cumulative drug dose more than 730 units  \* Users with cumulative drug dose more than 1095 units |

**Table 4**. Analyses to perform

## Output

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The covariates selected within the propensity score model, with associated coefficients will also be reported.

A plot showing the propensity score distributions for both cohorts after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score matching against the standardized mean difference for each covariate after propensity score matching.

An attrition diagram will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

The final outcome model, a Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

## Evidence Evaluation

We have executed diagnostics to determine if the analysis can be appropriately conducted. The diagnostics include:

* Propensity score distribution
* Covariate balance before and after propensity score matching
* Estimation for negative controls, to assess residual error
* Negative control exposures and outcomes will be used to evaluate the potential impact of residual systematic error in the study design, and to facilitate empirical calibration of the p-value and confidence interval for the exposures and outcome of interest.

Negative control outcomes in the context of this study are outcomes that are not believed to be caused by any H2RAs, and where therefore the true hazard ratio is equal to 1. We will execute the same analysis used for the primary hypothesis to produce hazard ratio estimates for the negative controls. The distribution of effect estimates across all negative controls will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target exposures and outcome of interest to calibrate the p-value.28

Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the traditional and empirically calibrated p-value and confidence interval for each negative control, as well as the hypothesis of interest.

## Data Sources

The analyses will be performed across a network of observational healthcare databases. All databases have been transformed into the OMOP Common Data Model, version 5. The complete specification for OMOP Common Data Model, version 5 is available at: <https://github.com/OHDSI/CommonDataModel>.

## Quality control

We will evaluate the PS by

* Inspection of the fitted PS model for large coefficients (indicative of model-misspecification) and predictors that we cannot explain (post-hoc).
* Inspection of the PS distribution.
* Evaluation of covariate balance after matching using the standardized difference in means between treatment and comparator cohort before and after matching. Standardized differences greater than 0.1 will be reported and investigated.

We will assess the feasibility of the study by identifying empirical equipoise

* Target and comparator cohorts are defined to stand in empirical equipoise, if the majority of patients in both carry preference scores between 0.3 and 0.7 and achieve sufficient balance if all after-adjustment baseline characteristics returned absolute standardized mean differences of less than 0.129

The error distribution estimated using the negative controls will be used to estimate residual bias after adjustments.

The CohortMethod package itself, as well as other OHDSI packages on which CohortMethod depends, use unit tests for validation.

## Strengths and Limitations of the Research Methods

Strength

* Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching and full outcome models allow balancing on a large number of baseline potential confounders.
* Use of negative control outcomes allow for evaluating the study design as a whole in terms of residual bias.

Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or misspecified confounders.

# Protection of Human Subjects

The study is using only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# Plans for Disseminating and Communicating Study Results

The study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

# References

1. Zeng T, Mitch WA. Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine. *Carcinogenesis*. 2016;37(6):625-634. doi:10.1093/carcin/bgw034

2. Mahase E. FDA recalls ranitidine medicines over potential cancer causing impurity. *BMJ*. 2019;367. doi:10.1136/bmj.l5832

3. Lin JK. Nitrosamines as potential environmental carcinogens in man. *Clin Biochem*. 1990;23(1):67-71. doi:10.1016/0009-9120(90)90489-h

4. Peto R, Gray R, Brantom P, Grasso P. Nitrosamine carcinogenesis in 5120 rodents: chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3, 6 or 20 weeks) and of species (rats, mice or hamsters). *IARC Sci Publ*. 1984;(57):627-665.

5. Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quartarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. *BMJ*. 2018;362. doi:10.1136/bmj.k3851

6. Tricker AR, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. *Mutat Res*. 1991;259(3-4):277-289. doi:10.1016/0165-1218(91)90123-4

7. Hecht SS. Approaches to cancer prevention based on an understanding of N-nitrosamine carcinogenesis. *Proc Soc Exp Biol Med Soc Exp Biol Med N Y N*. 1997;216(2):181-191. doi:10.3181/00379727-216-44168

8. Loh YH, Jakszyn P, Luben RN, Mulligan AA, Mitrou PN, Khaw K-T. N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study. *Am J Clin Nutr*. 2011;93(5):1053-1061. doi:10.3945/ajcn.111.012377

9. Zheng J, Stuff J, Tang H, Hassan MM, Daniel CR, Li D. Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study. *Carcinogenesis*. 2019;40(2):254-262. doi:10.1093/carcin/bgy169

10. Zhu Y, Wang PP, Zhao J, et al. Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada. *Br J Nutr*. 2014;111(6):1109-1117. doi:10.1017/S0007114513003462

11. Song P, Wu L, Guan W. Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis. *Nutrients*. 2015;7(12):9872-9895. doi:10.3390/nu7125505

12. La Vecchia C, D’Avanzo B, Airoldi L, Braga C, Decarli A. Nitrosamine intake and gastric cancer risk. *Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP*. 1995;4(6):469-474. doi:10.1097/00008469-199512000-00005

13. Tseng K-S, Lin C, Lin Y-S, Weng S-F. Risk of Head and Neck Cancer in Patients With Diabetes Mellitus: A Retrospective Cohort Study in Taiwan. *JAMA Otolaryngol Neck Surg*. 2014;140(8):746-753. doi:10.1001/jamaoto.2014.1258

14. Seo HJ, Oh I-H, Yoon S-J. A Comparison of the Cancer Incidence Rates between the National Cancer Registry and Insurance Claims Data in Korea. *Asian Pac J Cancer Prev*. 2012;13(12):6163-6168. doi:10.7314/APJCP.2012.13.12.6163

15. Kao C-H, Sun L-M, Liang J-A, Chang S-N, Sung F-C, Muo C-H. Relationship of Zolpidem and Cancer Risk: A Taiwanese Population-Based Cohort Study. *Mayo Clin Proc*. 2012;87(5):430-436. doi:10.1016/j.mayocp.2012.02.012

16. Abraha I, Serraino D, Giovannini G, et al. Validity of ICD-9-CM codes for breast, lung and colorectal cancers in three Italian administrative healthcare databases: a diagnostic accuracy study protocol. *BMJ Open*. 2016;6(3). doi:10.1136/bmjopen-2015-010547

17. El-Serag HB, Mason AC. Risk Factors for the Rising Rates of Primary Liver Cancer in the United States. *Arch Intern Med*. 2000;160(21):3227-3230. doi:10.1001/archinte.160.21.3227

18. Goldberg DS, Lewis JD, Halpern SD, Weiner MG, Re VL. Validation of a coding algorithm to identify patients with hepatocellular carcinoma in an administrative database. *Pharmacoepidemiol Drug Saf*. 2013;22(1):103-107. doi:10.1002/pds.3367

19. Jamal MM, Yoon EJ, Vega KJ, Hashemzadeh M, Chang KJ. Diabetes mellitus as a risk factor for gastrointestinal cancer among American veterans. *World J Gastroenterol WJG*. 2009;15(42):5274-5278. doi:10.3748/wjg.15.5274

20. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak*. 2015;15(1):31. doi:10.1186/s12911-015-0155-5

21. Esposito DB, Banerjee G, Yin R, et al. Development and Validation of an Algorithm to Identify Endometrial Adenocarcinoma in US Administrative Claims Data. Journal of Cancer Epidemiology. doi:https://doi.org/10.1155/2019/1938952

22. Lin H-W, Tu Y-Y, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol*. 2011;12(9):900-904. doi:10.1016/S1470-2045(11)70165-6

23. Won Y-J, Jung K-W, Oh C-M, et al. Geographical Variations and Trends in Major Cancer Incidences throughout Korea during 1999-2013. *Cancer Res Treat*. 2018;50(4):1281-1293. doi:10.4143/crt.2017.411

24. Porter MP, Kerrigan MC, Donato BMK, Ramsey SD. Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. *Urol Oncol Semin Orig Investig*. 2011;29(3):252-258. doi:10.1016/j.urolonc.2009.03.021

25. Luo R, Greenberg A, Stone CD. Outcomes of Clostridium difficile Infection in Hospitalized Leukemia Patients: A Nationwide Analysis. *Infect Control Hosp Epidemiol*. 2015;36(7):794-801. doi:10.1017/ice.2015.54

26. Sosa JA, Hanna JW, Robinson KA, Lanman RB. Increases in thyroid nodule fine-needle aspirations, operations, and diagnoses of thyroid cancer in the United States. *Surgery*. 2013;154(6):1420-1427. doi:10.1016/j.surg.2013.07.006

27. Voss EA, Boyce RD, Ryan PB, van der Lei J, Rijnbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. *J Biomed Inform*. 2017;66:72-81. doi:10.1016/j.jbi.2016.12.005

28. Schuemie MJ, Hripcsak G, Ryan PB, Madigan D, Suchard MA. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proc Natl Acad Sci*. 2018;115(11):2571-2577. doi:10.1073/pnas.1708282114

29. Walker AM, Patrick AR, Lauer MS, et al. A tool for assessing the feasibility of comparative effectiveness research. Comparative Effectiveness Research. doi:10.2147/CER.S40357

# Appendix: Concept Set Definitions

1. Bismuth or sucralfate

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 1036228 | Sucralfate | Drug | RxNorm | NO | NO | NO |
| 958134 | bismuth subcitrate | Drug | RxNorm | NO | NO | NO |

2. Cancer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 443392 | Malignant neoplastic disease | Condition | SNOMED | NO | YES | NO |

3. Gastric ulcer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Concept Id | Concept Name | Domain | Vocabulary | Excluded | Descendants | Mapped |
| 4265600 | Gastric ulcer | Condition | SNOMED | NO | YES | NO |

ICD10: K25.x; K28.x

ICD9-CM: 531.x; 533.3x; 534.x