Do Ranitidine and Nizatidine Increase the Risk of Gastrointestinal Cancer?

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A Master's Thesis
submitted to the
Department of Health Informatics & Biostatistics,
Graduate School of Public Health Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Public Health

HyeJung Kang

December 2021

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December 2021

ACKNOWLEDGEMENT

It's been over 2 years since I entered the graduate school of public health, and I'm finally submitting my thesis. Over the past 2 years, there are so many people who helped me and gave me a passion to keep studying. Through this paper, I would like to say thanks to everyone who encourage me.

Foremost, I am extremely grateful to my supervisor, Prof. Sohee Park for her invaluable supervision and support. Her knowledge and plentiful experience have encouraged me all the time. Also, I would like to express my special thanks to Prof. Chung Mo Nam for his wise insight and comments in all my school life. He always inspired me to think wise and study. On the way forward after graduation, I will always remember the teachings of two professors to grow as a better person.

I also thank Ph.D. Dong-Woo Choi for the advice and kindness to help me to analyze the data in my thesis. If there was no help from him, I couldn't get any precise results from the analysis. Moreover, I am very grateful to my best advisors, Hyun-Soo Zhang, and Wonjeong Jeong. Thank you for your all comments on my thesis. I could complete my problems through your solutions. Also, always thank you for your warm-heartedness, Jiyeon Chun and Jaeheon Yu.

And, I appreciate all my batch mates: Jung-Kwon Kim, Gyungnam Kim, Jieun Lee, Jieun Hwang, Yun-Ah Lee, Ye-Eun Kim, HyeBin Choi, Hyun-Jeong Jin, Hoyol Jang. I will never forget the times we spent together at school. I hope that there will be always a great future after your graduation.

Lastly, I want to give all my love and thanks to my family members. Jeju Kang, thank you for your support whenever I was in struggles. I could stand up strong through your encouragement. Eunhee You, you are the best mother I have ever seen in my life. I'm grateful that you are my mother. YoonJung Kang, also thank you for the support that you always gave me as food. Tae-Yun Kang, I'll never forget your advice all the time you gave me at school. In addition, all my friends who shared my happiness and also the sadness I had, I would like to express my gratitude that I can't put into words. Love you guys!

December, 2021
HyeJung Kang

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LIST OF ABBREVIATIONS

Abbreviation	Description
AOR	Adjusted odds ratio
BIC	Bayesian information criterion
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
CNORM	Censored normal model
DDD	Defined daily dose
DM	Diabetes mellitus
ECL	Enterochromaffin-like cells
FAERS	FDA Adverse Event Reporting System
FDA	US Food and Drug Administration
GBTM	Group based trajectory modeling
GERD	Gastroesophageal reflux disease
GI cancer	Gastrointestinal cancer
H2RAs	H2-receptor antagonists
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIRA	Health Insurance Service Review & Assessment service
HR	Hazard ratio
ICD-10	International Classification of Diseases
IFG	Impaired fasting glucose

Abbreviation	Description
IGT	Impaired glucose tolerance
KCD	Korean Standard Classification of Diseases
LCGA	Latent class growth analysis
LC-MS	Liquid chromatography-mass spectrometry
N/A	Not available
NHIS-NSC	National Health Insurance Service-National Sample Cohort
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PPIs	Proton pump inhibitors
ppm	Parts per million
PRRR	Proportionate reporting ratio
PSM	Propensity score matching
SMD	Standardized mean differences
WHO	World Health Organization
ZIP	Zero-inflated model

ABSTRACT

Do Ranitidine and Nizatidine Increase the Risk of Gastrointestinal Cancer?

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(Directed by Professor Sohee Park, Ph.D.)

Background: Gastrointestinal (GI) cancer develops in digestive organs such as the stomach, colon, liver, esophagus, and pancreas. About 83,034 cases of GI cancer was reported in Korea in 2020. Food habits of Korean individuals, such as consuming pickled vegetables such as kimchi and oily foods, and engaging in frequent drinking, could increase the risks of developing metabolic syndromes. Poor eating habits and stress increase the incidence of diseases such as gastroesophageal reflux disease, gastric ulcer, and gastritis in the human body, which can develop into GI cancer. However, in 2019, the US Food and

Drug Administration (FDA) reported that the drugs ranitidine and nizatidine contain N-nitrosodimethylamine, which is primarily used in industrial fields and is a known carcinogen. However, in subsequent studies, it could not be conclusively proven that ranitidine or nizatidine increased the risk of cancer. Accordingly, in this study, we used retrospective cohort data from Republic of Korea to investigate the effect of ranitidine and nizatidine intake on the development of GI cancer in Korean adults.

Methods: The data used in this study was a sample cohort of the National Health Insurance Corporation. The data is retrospective, constructed by extracting data from approximately 2% of the Korean population who are enrolled in health insurance. The data included people who did not die between 2002 and 2004, had no history of cancer, and had not previously claimed antihistamine receptor blockers (H2RAs). During the landmark period of 3 years, participants with 30 or more cumulative dosing days were subjected to propensity score matching. At this time, the exposed group was a person who had been prescribed ranitidine or nizatidine at least once during the exposure period, and the non-exposed group was a person who had never been prescribed these drugs. Thereafter, the defined daily dose (DDD) of ranitidine and nizatidine was calculated during the landmark period, and the groups were classified through trajectory analysis, following which the Cox regression analysis was performed. Secondly, the participants who developed GI cancer were defined as cases, and those who did not develop cancer were denoted as the control group. Matching was performed in the ratio 1:5 with the sex and age of the participants. Thereafter, conditional logistic regression analysis was performed.

Results: In the landmark study design, the results of Cox regression analysis using trajectory groups showed a statistically significant relationship with GI cancer risk. The "Moderate to slightly increased" users (HR=1.73, 95% CI=1.13-2.66) and the "Constantly high" users (HR=1.78, 95% CI=1.14-2.79) had a higher risk of GI cancer incidence. When subgroup analyses were performed, the "Constantly high" users (HR=2.09, 95% CI=1.04-4.09) and the "Moderate to slightly decreased" users (HR=2.29, 95% CI=1.11-4.76) had a higher risk of GI cancer in women (landmark period 1-year). Also, the "Moderate to slightly increased" users (HR=2.04, 95% CI=1.03-4.05) and the "Constantly high" users (HR=3.12, 95% CI=1.62-6.00) had a higher risk of GI cancer incidence in the participants who were below 60 years of age. However, no significant results were observed in the nested case-control study design.

Conclusions: This study tried to minimize biased results using various study designs and analysis methods. However, due to the nature of the data, there was a limitation in deriving the study results. In addition, ranitidine and nizatidine are over-the-counter (OTC) drugs that can be purchased without a prescription. Thus, there may be medication records that are not considered in the claimed data. However, an effort was made to minimize selection bias using a nested case-control study design. In future research, it will be possible to derive more advanced research results using the clinical variables, health screening data, and cancer registration data of the participants.

Key words: Gastrointestinal cancer, Ranitidine, Nizatidine, Trajectory analysis, Landmark analysis, Cox proportional hazards regression model, Nested case-control study, Conditional logistic regression

I. INTRODUCTION

1. Background

1.1 Gastrointestinal Cancer

The risk of gastrointestinal (GI) cancers is usually high in Asian countries. According to a previous study, GI cancers were commonly found to develop in the colon, rectum, stomach, liver, esophagus, and pancreas (Arnold et al., 2020). There were approximately 3.2 million GI cancer incidences in Asia (Figure 1) and 0.8 million in Korea in 2020 (Figure 2) (International Agency for Research on Cancer, 2020). A meta-analysis conducted in Korea and Japan showed that the habit of consuming salted vegetables increases the risk of stomach cancer (Kim et al., 2010). In addition, with western eating habits becoming common, the incidence of colorectal cancer is increasing (Park et al., 2016). Liver cancer, like other digestive cancers, occurs frequently in East Asia, but the main causative reason is different. Although lifestyle patterns, such as smoking and drinking, can promote its occurrence, infections by hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most well-known reason for its incidence (Mohammadian et al., 2018). Men are at a higher risk for developing esophageal cancer compared to women, and with the prevalence of smoking and alcohol consumption and reduced intake of fresh vegetables, there is an increased risk of developing gastroesophageal reflux disease (GERD) (Norat et al., 2014). In Korea, although the smoking rate is significantly decreasing, the prevalence of cancer among high-risk drinkers is increasing due to the high alcohol consumption rate (Jee et al., 2016).

Finally, a clear cause for pancreatic cancer, which is difficult to detect early due to the absence of early symptoms, has not yet been found. Presumed risk factors include smoking, alcohol consumption, eating habits, and characteristics such as body mass index (BMI), sex, age, and presence of diabetes mellitus (DM). Therefore, it is very important to elucidate the epidemiological mechanism of the cancers and explore more risk factors (Rawla, Sunkara and Gaduputi, 2019).

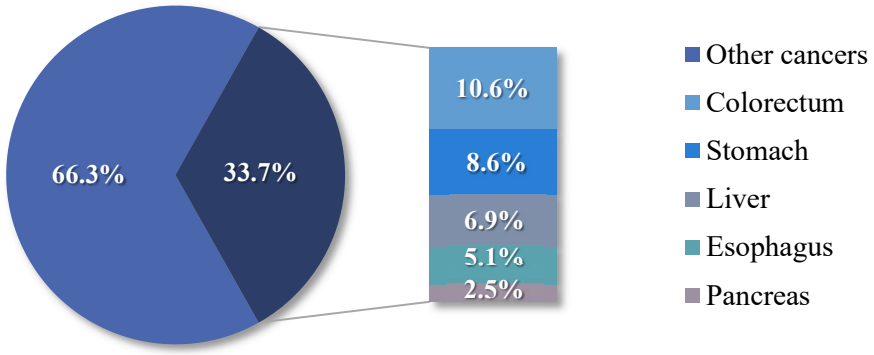

Figure 1. Estimated number of new cancer cases in Asia in 2020; both sexes, all ages

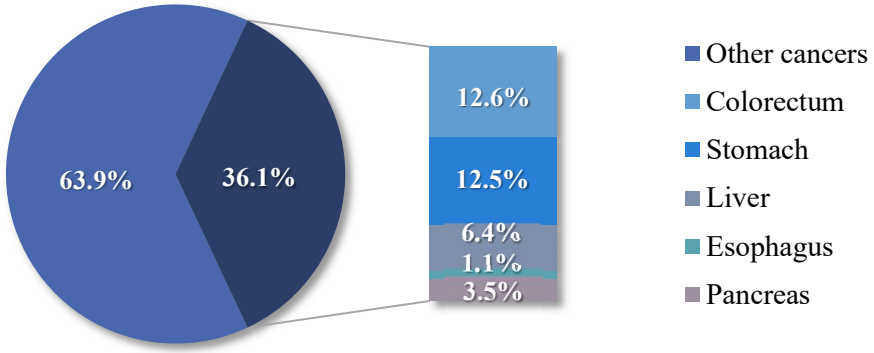

Figure 2. Estimated number of new cancer cases in Republic of Korea in 2020; both sexes, all ages

1.2 Ranitidine and Nizatidine

Ranitidine and nizatidine are antacids belonging to the H2-receptor antagonists (H2RAs) family, which have primarily been used to treat gastric ulcers or GERD. Both were Over-the-counter (OTC) and prescription drugs. Ranitidine, which is an aminomethyl furan derivative (Figure 3) inhibits gastric acid secretion by blocking histamine receptors in gastric parietal cells. It is generally absorbed in the small intestine, and the duration of action lasts about 8 to 12 hours (Zeldis, Friedman and Isselbacher, 1983). It has a half-life of 2.5 hours (Chau et al., 1982). Nizatidine, which is a hybrid structure of ranitidine and famotidine (Figure 4), is also absorbed into the body in a manner similar to that of ranitidine, and its effect lasts about 8 hours (Morton, 1987). The elimination half-life is between 1.1 and 1.6 hours (Price and Brogden, 1988).

However, in September 2019, the U.S. Food and Drug Administration (FDA) announced that a carcinogen called N-nitrosodimethylamine (NDMA) was detected in commercially available ranitidine and nizatidine. The substance is mainly used for industrial purposes (Sgroi et al., 2018), and is harmful to the human body, causing severe irritation to the eyes, vomiting, or abnormal liver function when ingested through inhalation, intake, or skin contact. The standard levels of NDMA prescribed by the FDA was 0.32 parts per million (ppm), but according to the lab data at the time, most ranitidine and nizatidine drugs showed higher levels than this value (U.S. Food and Drug Administration, 2019). The sample that showed the highest levels of NDMA contained approximately 2.85 ppm of the impurity. Therefore, the drugs were withdrawn from the pharmaceutical market and

replaced with other drugs in the same class, such as cimetidine, famotidine, roxatidine, and lafutidine, or with proton pump inhibitors (PPIs), which also reduce the stomach acid production.

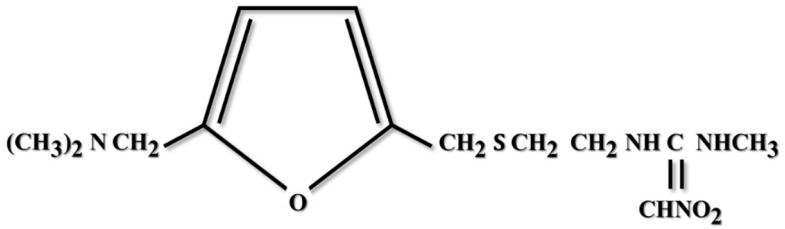

Figure 3. Chemical structure of ranitidine

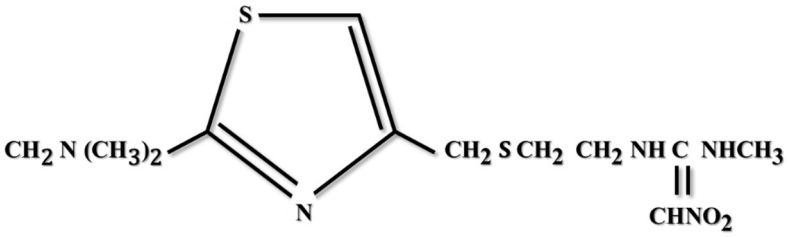

Figure 4. Chemical structure of nizatidine

2. Study objectives

In September 2019, ranitidine and nizatidine were withdrawn owing to the detection of carcinogens, and the controversy over the withdrawal continues till date. Therefore, this study aimed to analyze whether the drugs cause GI cancers in Korean individuals. Details of the study objectives are as follows:

1) To estimate the risk of GI cancer in accordance with the ranitidine and nizatidine intake.

2) To calculate the defined daily dose (DDD) of ranitidine and nizatidine and determine their latent trajectory groups.

3) To estimate the risk of GI cancer depending on the latent trajectory groups of ranitidine and nizatidine.

4) To estimate the risk of GI cancer depending on the average prescription days per year of ranitidine and nizatidine.

5) To evaluate the association between ranitidine, nizatidine, and GI cancer using risk-set matching and nested case-control study designs, and to compare the analysis results from the different study designs.

3. Literature review

3.1 Results from lab experiments

Two years after ranitidine was phased out for being a carcinogen, clinical trials for the drug were conducted in the United States. Healthy participants (non-smokers, non-drinkers, and non-drug users) between 18 and 50 years old were randomly divided and administered ranitidine (300 mg) and placebo drugs. They were further divided into the cured meat diet group and the noncured meat diet group to control for nitrates, which are known carcinogens. The primary outcome was to check the NDMA concentration through a urine test 24 hours after taking the drug. However, there was no statistically significant difference between the ranitidine group and the placebo group. The NDMA extraction levels of the ranitidine intake and placebo groups were 0.6 ng (Interquartile range; IQR=0–29.7) and 10.5 ng (IQR=0–17.8), respectively. This was contrary to the findings published by the FDA (Florian et al., 2021).

Simultaneously, an in-vitro study was conducted to determine whether ranitidine was a carcinogen. The research hypothesis of this study was that NDMA is produced when ranitidine interacts with the stomach acid. Therefore, 150 mg of ranitidine tablets were placed in 50 ml and 250 ml of simulated gastric fluid, respectively, and NDMA formation was observed. The nitrite concentrations were adjusted to 100 μmol/L and 10,000 μmol/L according to the pH level of the liquids. NDMA was measured using liquid chromatography-mass spectrometry (LC-MS). As a result of the study, NDMA was

detected 2 hours after adding ranitidine to the solution. However, the solution was very acidic compared to the gastric acid of the general population, and the concentration of nitrite was more than 5,000 μmol/L. Therefore, the previous study concluded that the results cannot be interpreted by applying them to the general population (Gao et al., 2021b).

3.2 Results from observational studies

The following studies were retrospectively conducted to confirm the association between ranitidine/ nizatidine and cancer incidence. Firstly, a study conducted in the United States used data from the FDA Adverse Event Reporting System (FAERS) from 2013 to 2020. It is a database established to monitor the safety of drugs post-marketing. Therefore, it contains information on the adverse effects that occurred after taking ranitidine. The outcome of the study was GI cancer, and PPIs were the control drugs. For the statistical analysis, the proportionate reporting ratio (PRRR) and 95% confidence interval (CI) were considered, and the difference between the two groups was confirmed using the Chi-squared test. A total of 13,856 people who took ranitidine experienced adverse events. Most of them were between 18 and 64 years old, and the proportion of women was 66.7%. Among the adverse event reports, the proportion of GI cancer was about 2.0%, and colorectal cancer accounted for the highest rate of 55.7% among the relevant carcinomas. The proportion of colorectal cancer among the GI cancer events of PPIs and other H2RAs, which were comparative drugs, was about 12.5%, and the incidence of the corresponding cancer was higher in those who took ranitidine ($p < .001$). Therefore, the study concluded

that the use of ranitidine may be associated with the development of GI cancer (McGwin, 2021).

The following studies were performed using the national health insurance claim data in Korea. In the first study, ranitidine was set as a case drug, and famotidine was used as a control drug. The study participants were those who took ranitidine or famotidine for 1 year or more between 2009 and 2011. People who used both drugs simultaneously were excluded. The two groups were matched 4:1 using their age, sex, presence of diabetes mellitus (DM), and cumulative duration of drug use during the exposure period. Outcome variables were the incidences of liver cancer, colorectal cancer, biliary cancer, gastric cancer, lung cancer, prostate cancer, kidney cancer, bladder cancer, uterine cancer, breast cancer, and thyroid cancer. The Cox proportional hazards regression analysis was performed to determine the cancer risk of the case group compared to the control group. However, there were no statistically significant results in any of the cancer types (Yoon et al., 2021).

Another study in Korea was conducted on people who had been taking H2RAs for 30 days or more between 2002 to 2008 and those who did not. Thereafter, the occurrence of gastric cancer was followed up until 2013. This study was also focused on adults. During the washout period, those who took PPIs, which could cause gastrointestinal disease when taken at high doses, were excluded. Also, patients with gastric diseases (polyps, erosion, ulcer) other than gastric cancer were excluded during the follow-up period. The study population was divided into three groups. Participants who took ranitidine or nizatidine

were defined as the case group, those who took the drugs of the same class were defined as the other H2RAs intake group, and those who did not take either of the drugs were the comparison group. The other H2RAs intake group and comparison group were matched 1:1 with the case group for age, sex, residential area, household income, disability, non-steroidal anti-inflammatory drugs (NSAIDs) dose, history of smoking, and alcohol. As a result of the Cox proportional hazards regression analysis, no statistically significant results were obtained in the case group (HR=1.02, 95% CI=0.87-1.20) and the other H2RAs intake group (HR=1.00, 95% CI=0.85-1.17) compared to the comparison group. Thus, there was no association between gastric cancer incidence and ranitidine and nizatidine intake (Kim et al., 2021).

II. METHODS

1. Data used

The data used in this study, National Health Insurance Service-National Sample Cohort (NHIS-NSC) version 1.0, was stratified and extracted by sex, age, social security status, income level, and location of residence among Koreans who were health insurance beneficiaries in 2002 (Figure 5). About 2.2% of the total population was extracted as the sample group. This data includes not only the Sociodemographical characteristics of the participants, but also information on all medical practices covered by health insurance (information on medical history, drug prescription, and health check-up) (Lee et al., 2017). It was updated from 2002 to 2013, and if there was a death, the participant was withdrawn from the cohort, and a new representative sample of newborns in the population in that year was added.

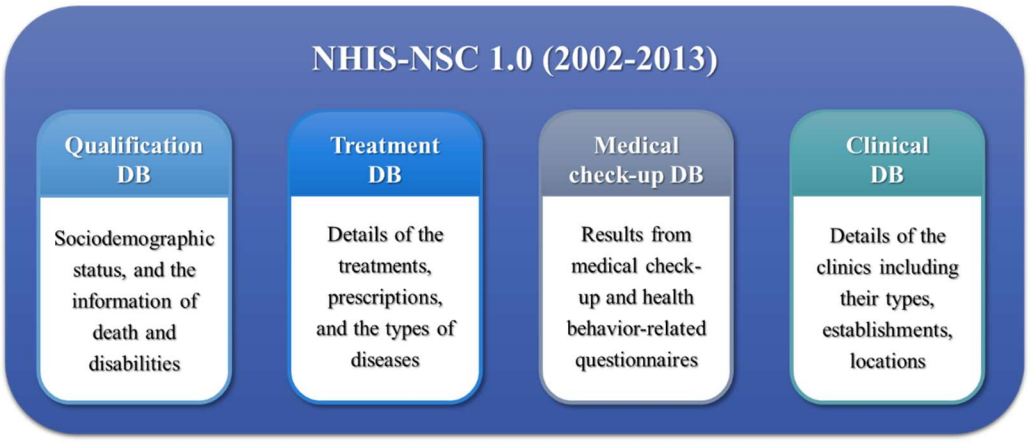

Figure 5. Description of NHIS-NSC 1.0

2. Study design

Two study designs were used and the results were compared to observe how the analysis results varied with the different designs. The first was a risk-set matching study design using landmark analysis, and the second was a nested case-control study design that matched cases and controls according to the occurrence of GI cancer.

2.1 Risk-set matching study

Landmark analysis was used to reduce the immortal time bias and make operational definitions of the participants in this study. This is the method of determining whether a specific event occured in patients who survived from the landmark period after treatment or drug administration (Anderson, Cain and Gelber, 1983; Dafni, 2011). The case and control defined at the baseline of the study can be changed over time, but if it is not considered, the immortal time bias can occur (Lévesque et al., 2010). Thus, by setting a landmark period, length bias can be removed, and an unbiased result can be derived (Gleiss, Oberbauer and Heinze, 2018). Those who developed cancer or died, and who had been taking H2RAs for less than 30 days during exposure period were excluded. In addition, participants were divided according to their exposure to ranitidine and nizatidine during the period. Propensity score matching (PSM) was performed with sociodemographic characteristics in their first year of taking H2RAs. Thereafter, the occurrence of GI cancer was observed during the follow-up period (Figure 6).

2.2 Nested case-control study

The nested case-control study design was utilized to investigate the association with the exposure to OTC drugs, and to reduce selection bias and immortal time bias. This is a more advanced design compared to the case-control study design, which defines a person with a disease as a case and a person who was exposed to the risk at the same time but did not develop the disease as a control (Ernster, 1994). It can be advantageous in pharmacoepidemiologic studies that follow up many participants over time and use time-dependent exposure such as drugs (Etminan, 2004). Thus, this design is suitable for this study using claim data in that it does not control the exposure of all participants to OTC drugs (Klepser, Collier and Cochran, 2013).

The participants of this design were those who had accumulated more than 30 days of administration for 3 years from the date of the first H2RAs. Cases represent the participants who first developed GI cancer during a period of 3 to 8 years from the first dose. Conversely, control is a person who has not developed cancer during that period (control may be a person who has developed GI cancer after that period). They were matched using the Sociodemographic characteristics of the case in the year of the GI cancer outbreak (Figure 7).

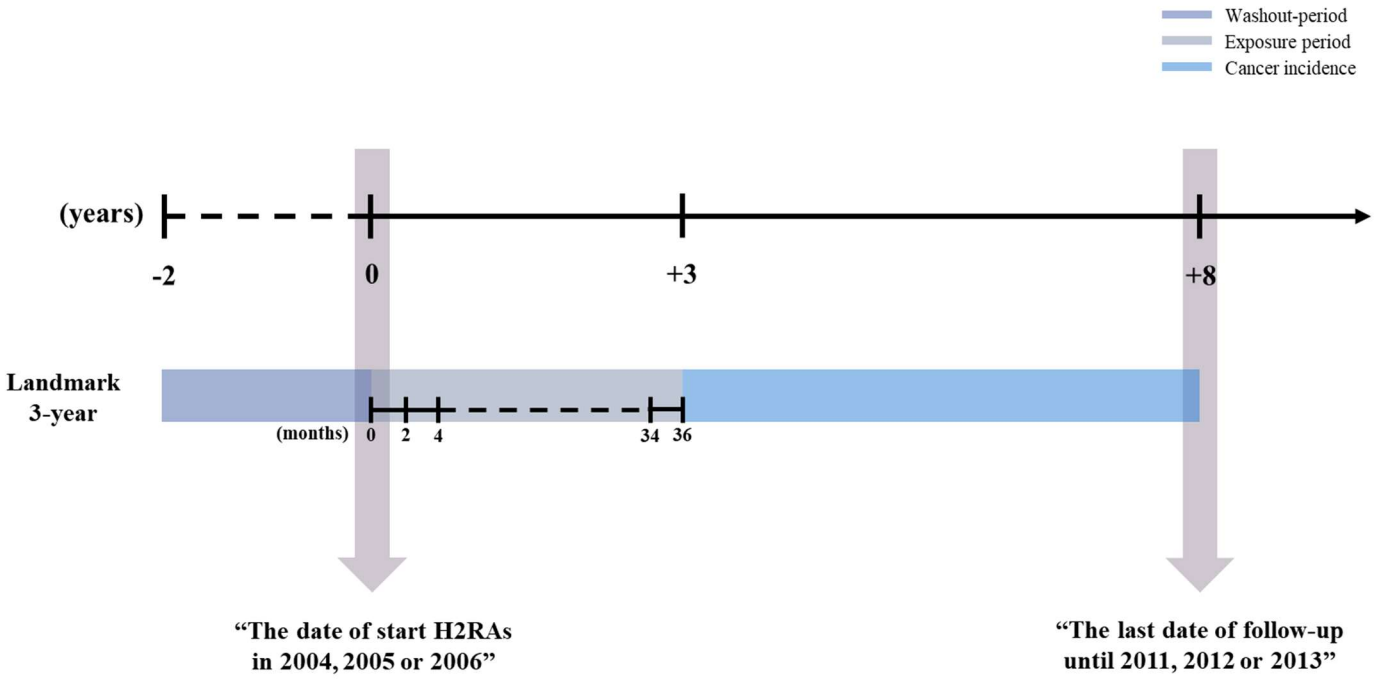

Figure 6. Timeline of risk-set matching study design

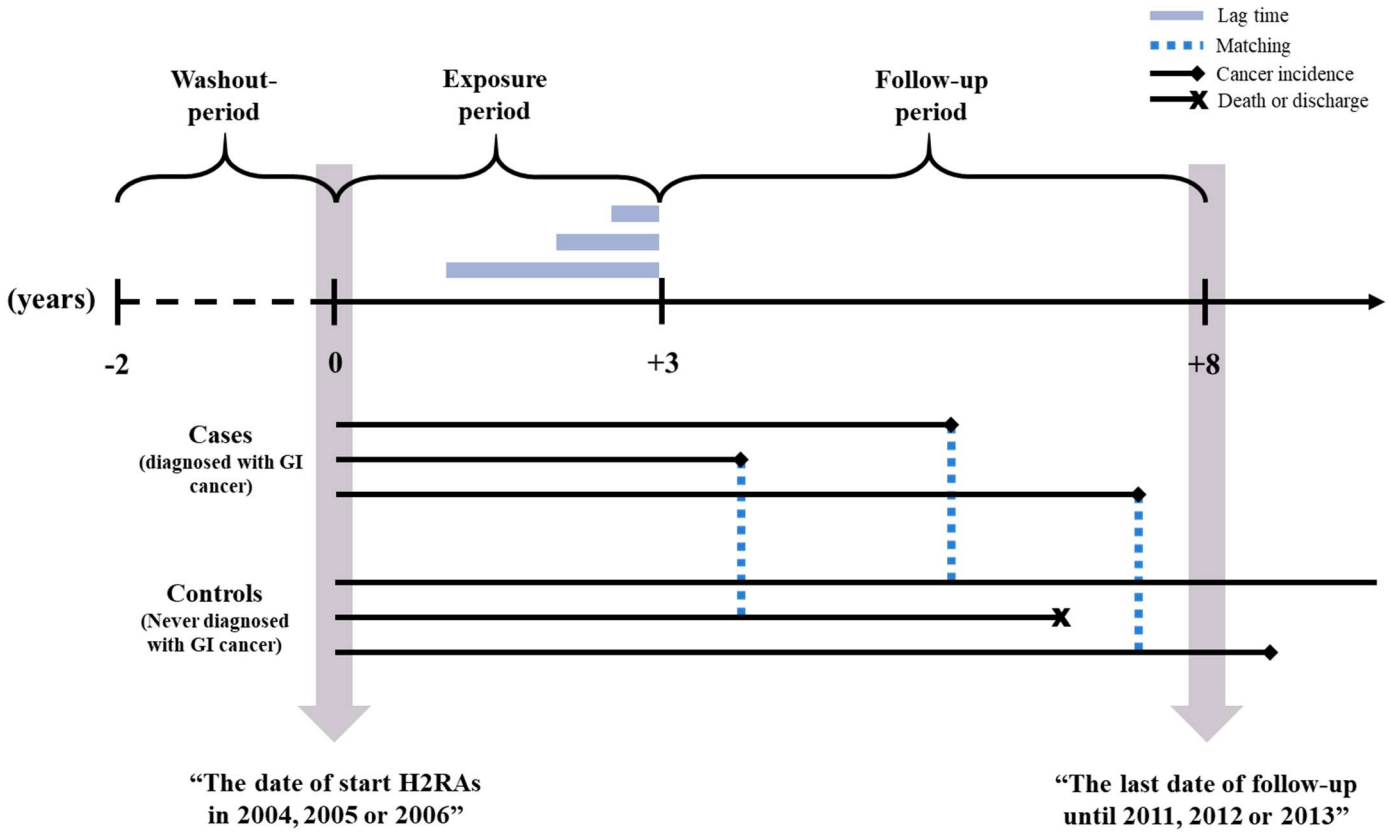

Figure 7. Timeline of nested case-control study design

3. Study population

The participants of this study were those who were prescribed H2RAs for the first time in 2004, 2005, or 2006, and have been taking H2RAs for more than 30 days during the exposure period. To identify the users of H2RAs, the therapeutic drug classification code provided by the Health Insurance Service Review & Assessment service (HIRA) was used. The code included 6 digits for core component and the last 3 alphabets indicated the administration route and dosage form (Table 1).

H2RAs are mainly administered by the oral (code 'A') or parenteral route (code 'B'). The drugs used in this study were ranitidine, nizatidine, cimetidine, famotidine, roxatidine, and lafutidine. All of these codes could be confirmed through the national reimbursement drug list of the HIRA, and even with the same component, the code could be different depending on the dose. For example, the code '222801ATB' and '222802BIJ' both contain ranitidine hydrochloride, but the code with '01ATB' is a 0.15 g dose tablet, and the code with '02BIJ' is a 28 mg dose injection (Table 2).

Table 1. Therapeutic drug classification from HIRA

	① ② ③ ④	⑤ ⑥	⑦	⑧ ⑨
Method	Unique number for core component in drug	Amount of the component	Administration route (A: oral, B: parenteral, C: topical, D: another route)	Dosage form

Table 2. H2RAs code from HIRA

Name of drug	Code
Ranitidine	222701ATB, 271800ATB, 222801ATB, 222802BIJ, 222803ATB, 222804BIJ, 222805ALQ, 222805ATB
Nizatidine	202701ACH, 202701ATB, 202703ACH, 202704ATB
Cimetidine	133301ATB, 133301BIJ, 133302ATB, 133303ATB, 133305ATR, 133301ACH, 133401ATR, 133304ATB
Famotidine	157301ATB, 157302ATB, 157302ACS, 157302ATD, 157302BIJ, 157303ATB, 157303ACS
Roxatidine	225201ACR, 225201ACH, 225202ACR, 225202ACH
Lafutidine	489302ATB

3.1 Risk-set matching study design

There were 1,004,097 people who entered the cohort in the year of 2002, 2003, or 2004. Among them, the people who never took H2RAs and who had experienced all types of cancer between the washout to exposure periods were excluded. Additionally, the participants who started taking H2RAs before 2004 or after 2006, and who were prescribed the drugs for less than 30 days during the exposure period and who were under 20 years of age were excluded. Therefore, 41,862 participants left in the landmark period of 3-year. The participants were divided into two groups depending on their exposure to ranitidine and/ or nizatidine. Thereafter, 1:1 ratio of PSM was performed with the sex, age, residential location, social security types, income, Charlson comorbidity index, cumulative DDD of PPIs, presence of DM, hypertension, dyslipidemia, and history of polypectomy. The Charlson comorbidity index was calculated during a year before the first intake of H2RAs.

And, the cumulative DDD of PPIs, presence of DM, hypertension, dyslipidemia, and history of polypectomy of the participants were calculated and gathered during the exposure period. The other sociodemographic characteristics of the participants were at the time of the first intake of H2RAs. Thus, 15,384 non-exposed and exposed participants remained respectively. 11,094 unmatched participants were excluded from the study (Figure 8).

3.2 Nested case-control study design

Similar to the risk-set matching study design, there were 1,004,097 people who entered the cohort in the year of 2002, 2003, or 2004. And, 91,299 participants who had never experienced H2RAs were excluded. Also, 655,747 participants who took H2RAs before or after exposure period and who died or had cancer during the washout to exposure period were excluded. The final participants (41,862) before PSM were over 20 years old at the time of the first dose and the cumulative number of days for which they had taken the drug during the exposure period was 30 days or more. Following this, a person who developed GI cancer during the follow-up period was defined as a case, and a person who did not develop cancer at the same time was a control. Cases and controls were matched as 1:5 ratios by age and sex at the time of onset of GI cancer. Finally, 634 cases and 3,170 controls remained for analysis (Figure 9).

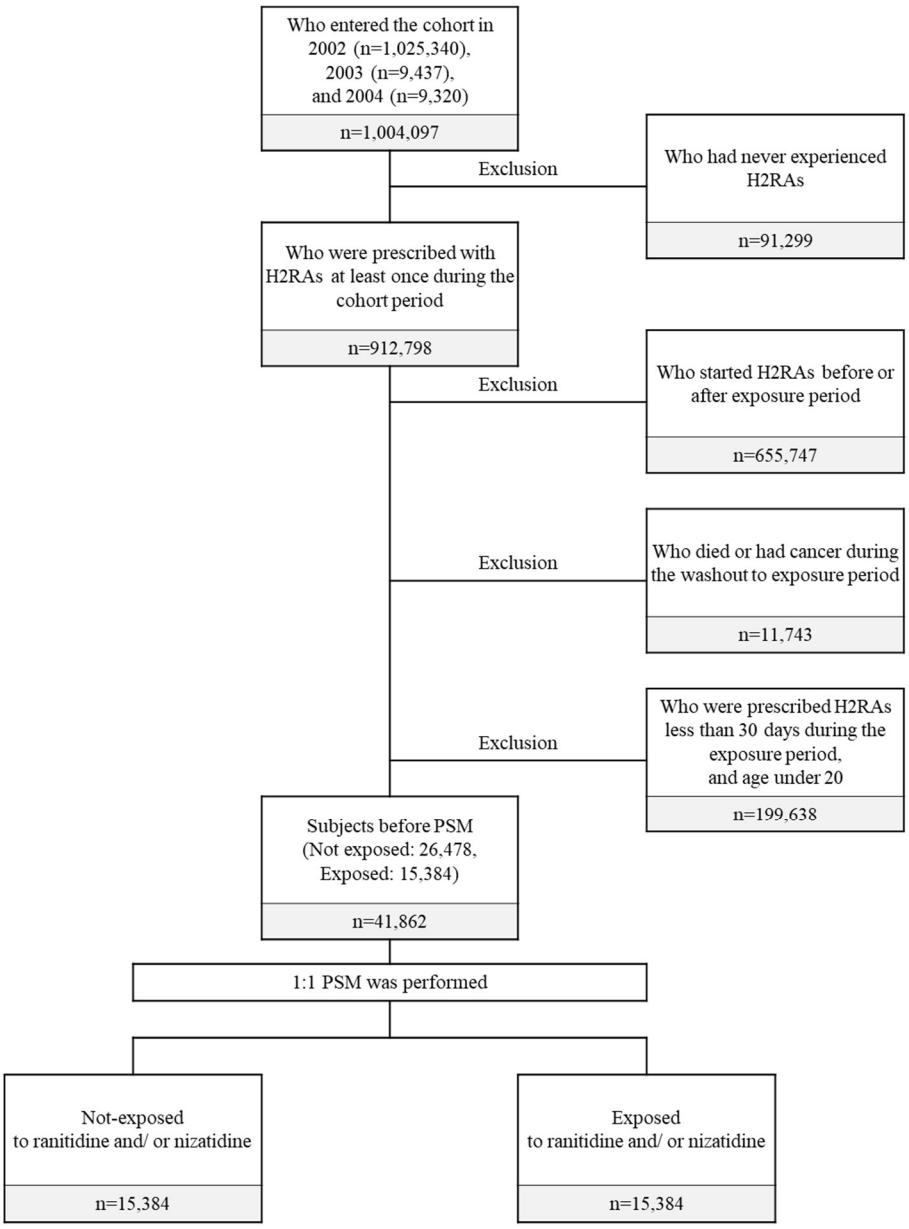

Figure 8. Flow chart of risk-set matching study design

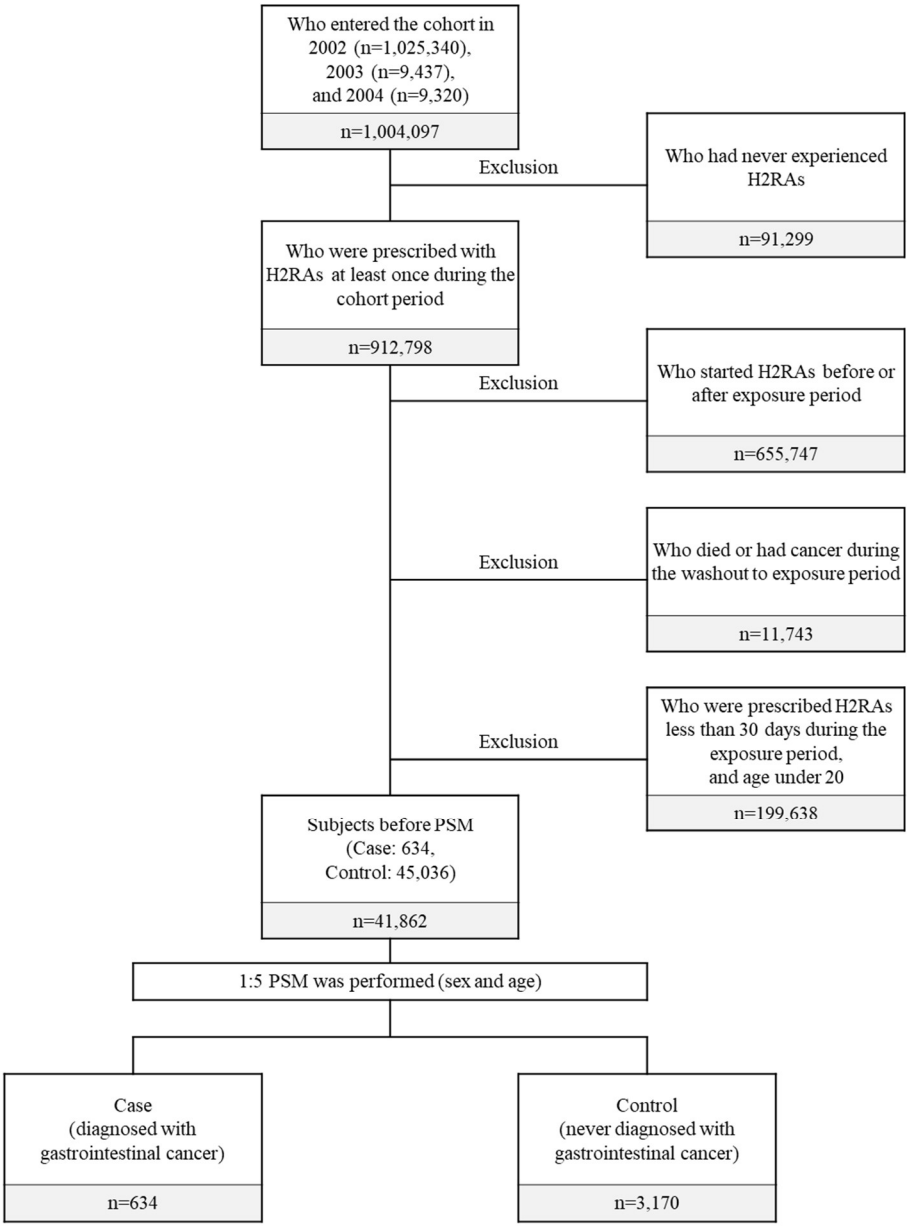

Figure 9. Flow chart of nested case-control study design

4. Variables

4.1 Outcome variables

Only the cases of GI cancer that occurred during the follow-up period (cancer incidence period in risk-set matching study timeline) was defined as the outcome of this study (Figure 8, 9). The Korean Standard Classification of Diseases (KCD) was used to define the cancer incidence (Table 3). It is used to classify diseases and other health problems in Korea and provides updates to the International Classification of Diseases (ICD-10) recommended by the World Health Organization (WHO).

Table 3. KCD code for gastrointestinal cancer

Cancer type	KCD code
Gastric cancer	C16
Colorectal cancer	C18, C19, C20
Liver cancer	C22
Esophagus cancer	C15
Pancreatic cancer	C25

4.2 Main interest variables

4.2.1 Defined daily dose (DDD)

Even if the components and dosage were the same, it would be very difficult to accurately measure the actual daily dose, because there is a difference in the amount that each person consumes per day. Therefore, in this study, DDD was used for unifying the different units of several H2RAs. DDD, which was developed by WHO, is a technical unit that means the average maintenance dose that one patient should take on a day for each component of the drug (WHO Collaborating Centre for Drug Statistics Methodology, 2018).

$$\mathrm{DDD}=\frac{(\text{Total amount of H2RAs used during 2 months}) \times (\text{Dose of H2RAs})}{\text{DDD defined by WHO}}$$

The DDDs of H2RAs for each landmark period were calculated by dividing by 3 months. DDD was calculated for each drug component and dose (Table 4).

Table 4. DDD of H2RAs defined by WHO

Name of drug	DDD	Unit
Ranitidine	0.3	g
Nizatidine	0.3	g
Cimetidine	0.8	g
Famotidine	40	mg
Roxatidine	150	mg
Lafutidine	20	mg

4.2.2 Average prescription days per year

In the nested case-control study design, average prescription days per year of ranitidine and nizatidine were calculated and used during the exposure period along with DDD. This value is the total number of prescription days over the 3 years of ranitidine and nizatidine, divided by the period from the first dose of H2RAs to the time of GI cancer, and multiplied by 365 days. In the formula below, the index date is the onset date of GI cancer. In the case of control, it was calculated by attaching the cancer onset date of the matched case. In addition, a potential lag period of 180 days was also considered during the period from which the drugs were taken to the onset of cancer. To test the accuracy of the lag period, sensitivity analysis was also performed by additionally setting 365 days and 730 days as lag periods (Lee et al., 2020b).

$$\text{Average days} = \frac{\text{Cumulative days of ranitidine and nizatidine use}}{(\text{Index date} - \text{lag period}) - \text{First date of H2RAs use}} \times 365$$

4.3 Covariates

4.3.1 Sociodemographic variables

NHIS-NSC 1.0 provided information on the basic socioeconomic characteristics of health insurance beneficiaries. The variables used in this study were sex, age, residential location, social security type, and income level. The age in the raw data was divided into 5-year units, but the age group taking H2RAs or developing digestive cancer was distributed in the middle-aged group. Therefore, the age of the participants was reclassified as 20–29 years old, 30–39 years old, 40–49 years old, 50–59 years old, 60 years old or older. In the case of location of residence, the region was divided into cities and provinces, but in this study, region was not a major variable, so it was divided into rural and urban areas. Urban areas included Seoul, Gyeonggi, and Incheon, and other areas were grouped into rural areas. Social security types were divided into three: medical aid beneficiaries, regional insurance beneficiaries, and corporate insurance beneficiaries, and income level was divided into quartiles.

4.3.2 Charlson Comorbidity Index

Although comorbidity may not be related to the main diagnosis, it is a very important covariate in that it can increase the mortality, length of stay, or medical expenses (Librero, Peiró and Ordiñana, 1999). The Charlson comorbidity index (CCI) was created in 1984 as a tool to predict patient mortality (Charlson et al., 1987). Using the tool, 19 diseases were selected based on medical records, and weights were assigned to each based on the relative risk of each disease (Kim, 2016) (Table 5). It is usually used with the ICD code, but in this study which used Korea's health claim data, KCD code was used to calculate. The weight can be assigned from a minimum of 1 point to a maximum of 6 points (Sundararajan et al., 2004). Based on the tool, the comorbidities experienced by the participants of this study one year before the exposure period were identified, and the CCI was calculated by assigning weights according to the disease. The corresponding CCI scores were used as a matching variable.

Table 5. Charlson Comorbidities Index

Comorbidity	KCD code	Weight
Myocardial infection	I21.x, I22.x, I25.2	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0	1
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x	1
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1	1
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	1
Rheumatologic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0	1
Peptic ulcer disease	K25.x–K28.x	1
Mild liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4	1
Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	1
Diabetes with chronic complication	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7	2
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9	2
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2	2
Any malignancy, including leukemia and lymphoma	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x	2
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	3
Metastatic solid tumor	C77.x–C80.x	6
AIDS/HIV	B20.x–B22.x, B24.x	6

4.3.3 Proton pump inhibitors

PPIs, like H2RAs, are antacids used to treat gastric ulcer, GERD, and gastritis. Unlike H2RAs, it is absorbed in the duodenum or small intestine and converted to sulfonamide in gastric parietal cells, where it inhibits gastric acid secretion (Yang and Metz, 2010). Although it has a stronger antacid action than H2RAs, side effects such as hypergastrinemia, gastric atrophy, and hyperplasia of enterochromaffin-like cells (ECL) occur when taken for a long period of time, which can lead to the development of cancer (McCarthy, 2020). Therefore, in this study, the intake of PPIs, which can be a confounding factor for the association between H2RAs intake and the occurrence of GI cancer, was controlled using annual DDD (Table 6).

Table 6. PPIs code from HIRA

Name of drug	Code
Omeprazole	204501BIJ, 204401ACE, 204401ATE, 204402ATE, 204403ATE
Lansoprazole	181301ACE, 181301ACH, 181301ATB, 181301ATD, 181301ATE, 181302ACH, 181302ATD, 181302ATE
Esomeprazole	459401BIJ, 509901ACH, 509902ACH, 527400ATB
Dexlansoprazole	621901ACR, 621902ACR
Rabeprazole	222201ATB, 222201ATE, 222202ATB, 222202ATE
Ilaprazole	505501ATE

4.3.4 Metabolic syndrome

In 1998, the WHO defined metabolic syndrome as the disease of insulin resistance with two or more accompanying symptoms (Alberti and Zimmet, 1998). Insulin resistance includes conditions such as type 2 diabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or other glucose-related impairments. Additional accompanying symptoms include taking antihypertensives, experiencing high blood pressure, having problems with plasma triglycerides, high-density lipoprotein (HDL) cholesterol or urinary albumin excretion, or having a BMI greater than 30 kg/m^2 (World Health Organization, 1999). In this study, metabolic syndrome was defined as DM, hypertension, and dyslipidemia. These diseases have been highly associated with cardiovascular disease (Isomaa et al., 2001) and death (Stepanova, Rafiq and Younossi, 2010). In addition, there was a study result that metabolic syndrome increases the risk of colorectal incidence (Lee et al., 2020a) and it was also associated with cancer-related mortality (Lee, Cho and Park, 2010). Therefore, in this study, if the KCD code specified in table 7 was confirmed at least once during the exposure period, it was defined as a patient suffering from the disease, and they were used as controlled factors in the analyses.

Table 7. KCD code for metabolic syndrome

Disease	KCD code
Diabetes mellitus	E10, E11, E12, E13, E14
Hypertension	I10, I11, I12, I13, I14, I15
Dyslipidemia	E78

4.3.5 Polypectomy

A polyp refers to an abnormal proliferation of the mucous membrane of the stomach, colon, rectum, vocal cords, or uterus. In Korea, it is mainly diagnosed using gastroscopy and colonoscopy during health examinations. According to a previous study, the number of patients who underwent polypectomy after a polyp was found during colonoscopy significantly increased for 12 years in all genders and ages (Cha et al., 2020). Although benign polyps are not cancerous cells, they can later turn into malignant cells; therefore, early removal is important depending on their size. Therefore, polypectomy is considered to be one of the factors that can affect the occurrence of GI cancer. In this study, using the master file of codes on medical practice provided by HIRA, it was checked whether the participants had received digestive-related polypectomy in areas such as the stomach, colon, biliary, and pancreas at least once during exposure period (Table 8).

Table 8. Polypectomy code from HIRA

Surgery	Code
Gastric polyps	Q2521
Colorectal polyps	Q2645, Q7701, Q7751
Biliary or pancreatic polyps	Q7766, Q7775

5. Statistical analysis

5.1 Propensity score matching

In a clinical trial comparing the difference in performance or efficacy between two drugs, cases and controls are randomly assigned to minimize bias that may affect the comparison. However, in a retrospective study like this study, complete randomization is difficult (Lee, 2016) and confounding effects are difficult to reduce (Austin, 2011). Therefore, the PSM method was devised. The propensity score is calculated based on the baseline characteristics of the study participants which can be Sociodemographic variables, clinical variables, or others (Rosenbaum and Rubin, 1983). Thus, selection bias can be controlled which is an increase in the probability that a participant belongs to a specific group due to covariates. Before matching, the propensity scores of the participants are obtained through logistic regression analysis. In this study, the sex, age, residential location, social security status, income level, and CCI of the participants were used in the logistic model to produce the scores. The score has a value between 0 and 1. Then, the propensity scores of participants in the case group are paired with the scores of participants in the control group. In this process, the researcher can determine the ratio that suits his/her research design. In this study, matching was performed using a ratio of 1:1 for the risk-set matching study design and 1:5 for nested case-control study design.

$$\text{logit}(\text{P}(\text{Z}=\text{Exposed})) = \alpha + \beta_1\text{sex} + \beta_2\text{age} + \beta_3\text{region} + \beta_4\text{insurance} + \beta_5\text{income} + \beta_6\text{CCI}$$

5.2 Group based trajectory analysis

In the risk-set matching study design, the H2RAs DDD of the participants was calculated during the exposure period, and the pattern of change over time was identified, divided into groups, and applied to the Cox proportional hazard model. Group based trajectory modeling (GBTM) classifies progress patterns according to specific variables that change over time into several groups. The analysis method is considered as a growth model in that it aims to analyze changes in the dependent variable. In addition, it can be considered as a latent class model in that it divides potential layers. This is a hybrid of the growth model and latent class model, called the latent class growth analysis (LCGA) and is one of the GBTM techniques (Jung and Wickrama, 2008). The analysis method varies depending on the type of data. For binary data coded as 0 and 1, the logit model is applied. The zero-inflated model (ZIP) is applied to the count data with a very high frequency of 0, and finally, the censored normal model (CNORM) is applied to the psychometric scale data. In this study, the CNORM type was utilized. The analysis method can be used in software such as Mplus, STATA, and SAS. In this study, the analysis was performed using the PROC TRAJ procedure option of SAS software, which was downloaded from https://www.andrew.cmu.edu/user/bjones. The following formula describes the model assumption. i is expressing individuals, and y_i is expressing the trajectory patterns over time. Then, z_i represents the baseline covariates. i, y_i, z_i should be independent with C_i which is the latent group (Gao et al., 2021a).

$$f(y_i|z_i) = \sum_{k=1}^{K} Pr(C_i = k|z_i)\, Pr(y_i|\, C_i = k, z_i)$$

$$= \sum_{k=1}^{K} \frac{\exp(\theta_k + \lambda_k^T z_i)}{\sum_{l=1}^{k} \exp(\theta_l + \lambda_l^T\, z_i)} Pr(y_i|\, C_i = k, z_i)$$

Following this, a modeling fitting procedure should be performed to find the appropriate number of trajectory groups. Firstly, the Bayesian information criterion (BIC) (Kass and Wasserman, 1995) score was checked with the lowest number of trajectory group and order equation (Jones, Nagin and Roeder, 2001). SAS provides 4 types of order equation which includes 0 (intercept), 1 (linear), 2 (quadratic), and 3 (cubic). In addition, the trajectory pattern graph can be checked to determine the number of groups showing the most appropriate shape. In this study, the BIC log Bayes factor approximation, a method to confirm BIC using null model and complex model, was selected (Kass and Raftery, 1995).

$$2\log_e(B_{10}) \approx 2(\triangle BIC)$$

5.3 Cox proportional hazard regression analysis

This model is one of the survival analysis methods, and differs from the Kaplan-Meier survival analysis and log-rank test in that the analysis can be performed on the risk factors affecting survival and covariates can be adjusted (Dudley, Wickham and Coombs, 2016). In addition, the Kaplan-Meier survival analysis and log-rank test are nonparametric analysis methods, but Cox proportional hazard regression analysis is a semi-parametric statistical method. It has nonparametric characteristics in that it does not require a specific assumption for survival time, but it also has parametric characteristics because it can be expressed using a specific formula when a covariate is provided. The model requires the assumption that the survivor function follows an exponential function, and the proportional hazards assumption that the hazard ratio of the two groups remains constant throughout the study period (Cox, 1972). The hazard ratio can be calculated through the hazard rate of the case group and the control group. Cox proportional hazard regression analysis was performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA), and Kaplan-Meier survival plots were drawn using R software version 4.0.2.

5.4 Conditional logistic regression analysis

If case-control matching is performed in a cohort study, conditional logistic regression analysis should be performed. This model is the extended version of logistic regression, and the main difference is that the model considers the strata of the participants (Breslow et al., 1978). The number of strata depends on the size of the participants used in the analysis. β can be estimated through the formula below using maximum likelihood. If j_i is the case in the *i*th matched set, $\underset{\sim}{\gamma}$ maximizes $L = \prod_{i=1}^{S} P_{ij_i}$ (Rosner, 2015). Conditional logistic regression analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

$$P_{ij} = \Pr\left(D_{ij} = 1 \middle| \sum_{k=1}^{ni} D_{ik} = 1\right) = \frac{\Pr(D_{ij} = 1) \prod_{k=1, k\neq j}^{ni} \Pr(D_{ik} = 0)}{\sum_{l=1}^{ni} \Pr(D_{il} = 1) \prod_{k\neq l}^{ni} \Pr(D_{ik} = 0)}$$

$$= \frac{\exp\left(\alpha_i + \beta x_{ij} + \underset{\sim\sim}{\gamma z}_{ij}\right) / \prod_{k=1}^{ni}[1 + \exp(\alpha_i + \beta x_{ik} + \underset{\sim\sim}{\gamma z}_{ik})]}{\prod_{l=1}^{ni} \exp(\alpha_i + \beta x_{il} + \underset{\sim\sim}{\gamma z}_{il}) / \prod_{k=1}^{ni}[1 + \exp(\alpha_i + \beta x_{ik} + \underset{\sim\sim}{\gamma z}_{ik})]}$$

$$= \frac{\exp(\beta x_{ij} + \underset{\sim\sim}{\gamma z}_{ij})}{\sum_{l=1}^{ni} \exp(\beta x_{il} + \underset{\sim\sim}{\gamma z}_{il})}$$

III. RESULTS

1. Risk-set matching study with landmark analysis

1.1 Characteristics of study participants

There were 41,862 participants before PSM, and 30,768 left after matching. Standardized mean differences (SMD) was checked, and the absolute values of all matching variables were less than 0.1. Firstly, the percentage of women was higher in the exposed group, but it was not significant (exposed=54.9%, exposed=54.7%, p=0.757). The younger participants were more distributed in the exposed group. The percentage of participants who were aged 60 and above was lower in the exposed group and it was statistically significant (non-exposed=26.1%, exposed=23.6%, $p < 0.001$). Additionally, the percentage of participants who were living in the urban area was higher in the non-exposed group (non-exposed=48.4%, exposed=43.2%, $p < 0.001$). The percentage of participants with employee insurance was higher in the exposed group (non-exposed=56.1%, exposed=57.6%, $p < 0.001$). In the case of income, there was no significant difference between non-exposed and exposed groups. The participants with CCI scores of 3 or more were significantly higher in the exposed group (non-exposed=6.5%, exposed=7.5%, $p < 0.001$). For the cumulative DDD of PPIs, the percentage of nonusers was higher in the non-exposed group (non-exposed=89.5%, exposed=75.9%, $p<0.001$). Lastly, the percentages of DM (non-exposed=14.6%, exposed=14.8%, p=0.692), hypertension (non-exposed=29.8%, exposed=30.4%, p=0.204), dyslipidemia (non-

exposed=14.3%, exposed=17.0%), and history of polypectomy (non-exposed=1.4%, exposed=2.3%) were all higher in the exposed group. However, the only p-values from dyslipidemia ($p < 0.001$) and polypectomy ($p < 0.001$) were significant (Table 9).

The percentage of participants who were taking PPIs more than 100 DDD was higher in the non-exposed group after matching (non-exposed=0.8%, exposed=0.2%, $p<0.001$). However, there was no significant association on the presence of DM. Lastly, the percentages of hypertension (non-exposed=29.8%, exposed=31.0%, $p=0.016$), dyslipidemia (non-exposed=14.3%, exposed=16.9%, $p<0.001$), and polypectomy (non-exposed=1.4%, exposed=2.2%, $p<0.001$) were still higher in the exposed group (Table 9).

During the follow-up period after 3 years, GI cancers occurred in 1.4 % of the non-exposed group and 1.6% of the exposed group ($p=0.426$). The percentages of gastric cancer and colorectal cancer were both 0.5% in the non-exposed and exposed groups (all $p > 0.050$). Next, liver cancer occurred in 0.2% and 0.4% in the two groups ($p=0.010$). However, the incidences of esophageal cancer and pancreatic cancer were not different between the two groups (all $p > 0.050$) (Table 10).

Table 9. Sociodemographic characteristics of participants before and after PSM

Variables	Exposed to ranitidine and/ or nizatidine							
	Before matching				*p**	After matching				*p**
	Non-exposed (n=15,384)		Exposed (n=26,478)			Non-exposed (n=15,384)		Exposed (n=15,384)		
	n	(%)	n	(%)		n	(%)	n	(%)	
Sex†					0.757					0.819
Male	6,945	(45.1)	11,996	(45.3)		6,945	(45.1)	6,924	(45.0)	
Female	8,439	(54.9)	14,482	(54.7)		8,439	(54.9)	8,460	(55.0)	
Age†					<0.001					0.996
20~29	1,833	(11.9)	3,188	(12.0)		1,833	(11.9)	1,810	(11.8)	
30~39	2,963	(19.3)	4,880	(18.4)		2,963	(19.3)	2,967	(19.3)	
40~49	3,636	(23.6)	6,623	(25.0)		3,636	(23.6)	3,647	(23.7)	
50~59	2,937	(19.1)	5,538	(20.9)		2,937	(19.1)	2,937	(19.1)	
≥60	4,015	(26.1)	6,249	(23.6)		4,015	(26.1)	4,023	(26.2)	
Region†					<0.001					0.973
Rural	7,935	(51.6)	15,040	(56.8)		7,935	(51.6)	7,939	(51.6)	
Urban	7,449	(48.4)	11,438	(43.2)		7,449	(48.4)	7,445	(48.4)	
Social security†					<0.001					0.710
Medical aid	52	(0.3)	54	(0.2)		52	(0.3)	44	(0.3)	
Insurance (Regional)	6,703	(43.6)	11,168	(42.2)		6,703	(43.6)	6,695	(43.5)	
Insurance (Corporate)	8,629	(56.1)	15,256	(57.6)		8,629	(56.1)	8,645	(56.2)	
Income†					0.960					0.992
Low	2,340	(15.2)	3,994	(15.1)		2,340	(15.2)	2,328	(15.1)	
Lower middle	3,905	(25.4)	6,697	(25.3)		3,905	(25.4)	3,927	(25.5)	
Upper middle	4,987	(32.4)	8,584	(32.4)		4,987	(32.4)	4,981	(32.4)	
High	4,152	(27.0)	7,203	(27.2)		4,152	(27.0)	4,148	(27.0)	

(continued)

Table 9. Sociodemographic characteristics of participants before and after PSM (continued)

Variables	Exposed to ranitidine and/ or nizatidine								
	Before matching				*p**	After matching			*p**
	Non-exposed (n=15,384)		Exposed (n=26,478)			Non-exposed (n=15,384)		Exposed (n=15,384)	
	n	(%)	n	(%)		n	(%)	n	(%)	
CCI†					<0.001				0.695
0	11,392	(74.1)	18,770	(70.9)		11,392	(74.1)	11,411	(74.2)	
1	2,997	(19.5)	5,734	(21.7)		2,997	(19.5)	3,014	(19.6)	
≥2	995	(6.5)	1,974	(7.5)		995	(6.5)	959	(6.2)	
Cumulative DDD of PPIs					<0.001				<0.001
Nonusers	13,770	(89.5)	20,090	(75.9)		13,770	(89.5)	11,677	(75.9)	
<50 DDD	1,268	(8.2)	4,691	(17.7)		1,268	(8.2)	2,721	(17.7)	
50~99 DDD	229	(1.5)	1,140	(4.3)		229	(1.5)	671	(4.4)	
≥100 DDD	117	(0.8)	557	(2.1)		117	(0.8)	315	(2.0)	
Diabetes Mellitus					0.692				0.859
No	13,132	(85.4)	22,563	(85.2)		13,132	(85.4)	13,144	(85.4)	
Yes	2,252	(14.6)	3,915	(14.8)		2,252	(14.6)	2,240	(14.6)	
Hypertension					0.204				0.016
No	10,805	(70.2)	18,439	(69.6)		10,805	(70.2)	10,610	(69.0)	
Yes	4,579	(29.8)	8,039	(30.4)		4,579	(29.8)	4,774	(31.0)	
Dyslipidemia					<0.001				<0.001
No	13,191	(85.7)	21,978	(83.0)		13,191	(85.7)	12,778	(83.1)	
Yes	2,193	(14.3)	4,500	(17.0)		2,193	(14.3)	2,606	(16.9)	
Polypectomy					<0.001				<0.001
No	15,173	(98.6)	25,861	(97.7)		15,173	(98.6)	15,041	(97.8)	
Yes	211	(1.4)	617	(2.3)		211	(1.4)	343	(2.2)	

Abbreviation: CCI, Charlson comorbidity index; DDD, Defined daily dose; PPIs, Proton pump inhibitors

* p-value from Chi-squared test

† Variables used for propensity score matching analysis

Table 10. GI cancer incidence depends on the binary exposure

Cancer types	Exposed to ranitidine and/ or nizatidine				*p**
	Not exposed (n=15,384)		Exposed (n=15,384)		
	n	(%)	n	(%)	
Overall cancer					0.426
No	15,161	(98.6)	15,143	(98.4)	
Yes	223	(1.4)	241	(1.6)	
Gastric cancer					0.694
No	15,300	(99.5)	15,306	(99.5)	
Yes	84	(0.5)	78	(0.5)	
Colorectal cancer					0.686
No	15,304	(99.5)	15,310	(99.5)	
Yes	80	(0.5)	74	(0.5)	
Liver cancer					0.010
No	15,346	(99.8)	15,319	(99.6)	
Yes	38	(0.2)	65	(0.4)	
Esophageal cancer					0.773
No	15,379	(100.0)	15,377	(100.0)	
Yes	5	(0.0)	7	(0.0)	
Pancreatic cancer					1.000
No	15,366	(99.9)	15,365	(99.9)	
Yes	18	(0.1)	19	(0.1)	

* P-value from chi-squared test and Fisher's exact test

1.2 Results from survival analyses with binary exposure

As a result of the Kaplan-Meier survival analysis, it was found that the cumulative incidence gradually increased from the landmark period to the time of the final observation, but the incidence rates of the non-exposed and exposed groups were intertwined. Moreover, using the log-rank test, it was confirmed that the finding was not statistically significant (p=0.420) (Figure 10). Therefore, additional log-log plot was drawn (Figure S1).

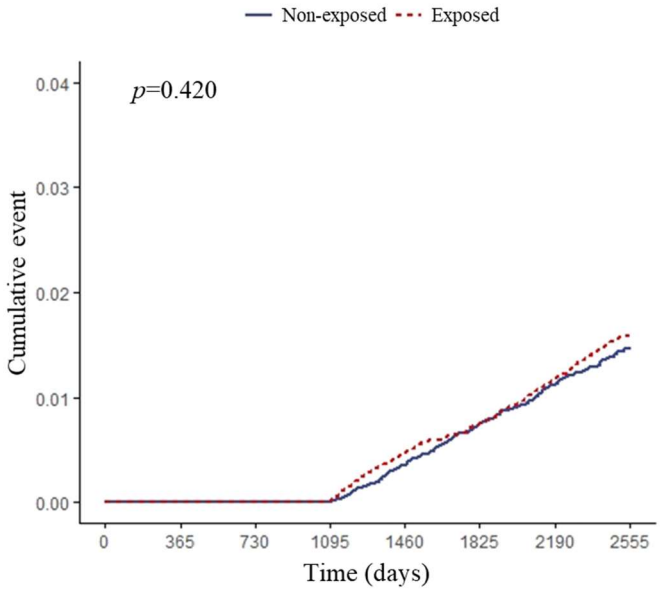

Figure 10. Kaplan-Meier survival curve with binary exposure

However, even in the log-log plot, the two groups seemed to overlap each other, and did not show a parallel relationship. Accordingly, the proportional hazards assumption for performing the Cox regression analysis was not satisfied. However, Cox regression analysis was additionally performed to confirm the results when the sociodemographic variables of

the participants were controlled, and to examine how the variables affected the occurrence of GI cancer. As a result of the Cox regression analyses, there was no significant association between ranitidine and/ or nizatidine exposure and GI cancer incidence (HR=1.05, 95% CI=0.87-1.26). But, the risk was higher in the participants who were taking 50~99 DDD of PPIs (HR=1.66, 95% CI=1.09-2.54), and the participants with DM had a higher risk of developing GI cancer (HR=1.99, 95% CI=1.61-2.47). In addition, the participants with hypertension had a higher risk of cancer (HR=1.75, 95% CI=1.43-2.13). Likewise, the participants who experienced polypectomy had a higher risk of developing GI cancer (HR=1.69, 95% CI=1.02-2.78) (Table 11). The power of the analysis was 13.0%.

Table 11. Cox regression analyses with binary exposure

Variables	Gastrointestinal cancer (n=30,768)	
	HR	**95% CI**
Ranitidine and/ or nizatidine		
Not exposed	1.00	
Exposed	1.05	0.87 - 1.26
Cumulative DDD of PPI		
Nonusers	1.00	
<50 DDD	0.96	0.73 - 1.27
50~99 DDD	1.66	1.09 - 2.54
≥100 DDD	1.27	0.65 - 2.46
Diabetes Mellitus		
No	1.00	
Yes	1.99	1.61 - 2.47
Hypertension		
No	1.00	
Yes	1.75	1.43 - 2.13
Dyslipidemia		
No	1.00	
Yes	0.95	0.75 - 1.21
Polypectomy		
No	1.00	
Yes	1.69	1.02 - 2.78

Abbreviation: HR, Hazard ratio; CI, Confidence interval; DDD, Daily defined dose; PPI, Proton pump inhibitor

1.3 Results from trajectory analyses

To find the most appropriate number of trajectories in the exposed group, BIC values and graphs from the trajectory analyses were checked. Groups were determined through the lower BIC values, the higher number of groups, and the high order equations. It was confirmed that 5 groups were selected through the steps mentioned above (Table 12). Following this, each group name was assigned based on the graph and average DDD. Trajectory groups were divided into "Nonuser," "Constantly low," "Moderate to slightly decreased," "Low to sharply increased," and "Constantly high" (Figure 11).

Table 12. BIC and $2\log_e$ (B_{10}) for selecting the best model

Number of Groups	Order equation*	Monthly DDD of ranitidine and/ or nizatidine		
		BIC	Null Model	$2\log_e$
2	0 3	-683214.2		
3	0 3 3	-663075.2	2	40278.0
4	0 3 3 3	-655799.8	3	14550.8
5	**0 0 0 3 3**	**-654989.9**	**4**	**1619.8**
6	0 0 0 1 0 3	-656322.2	5	-2664.6

Abbreviation: DDD, Defined daily dose; BIC, Bayesian information criterion
* Order equation: 0=Intercept, 1=Linear, 2=Quadratic, 3=Cubic

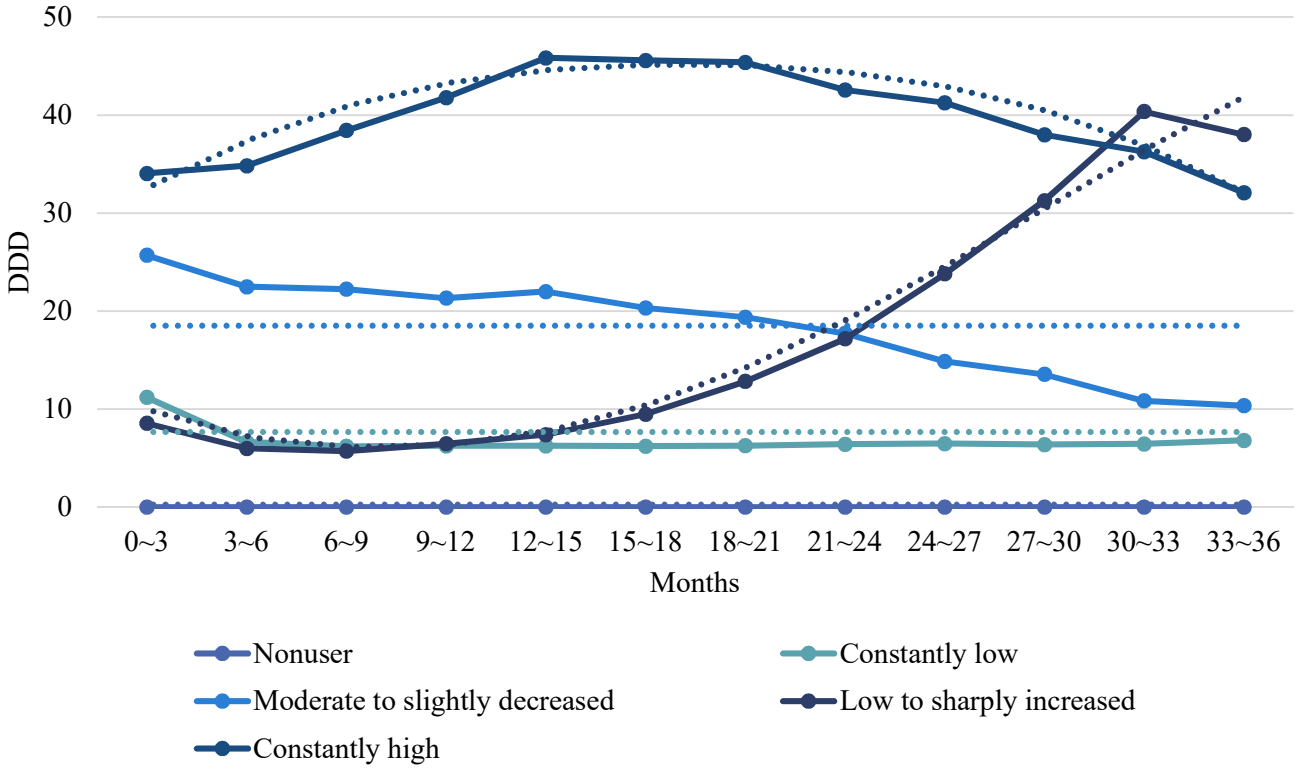

Figure 11. Trajectory graph of exposed group

1.4 Characteristics of each trajectory groups

The participants were distributed into 5 groups. Firstly, there were 15,384 in the "Nonuser" group, 14,204 participants were in the "Constantly low" group, 545 participants were in the "Moderate to slightly decreased" group, 451 were in the "Low to sharply increased," group and 184 were in the "Constantly high" group. Firstly, 54.9% of participants belonging to "Nonuser" were women, and the percentage of individuals aged over 60 years was the highest with 26.1%. The participants living in rural areas were 51.6%, and those with employee insurance were 56.1%. Most of them belonged to the upper-middle-income level (32.4%), and those with a CCI score of 2 or more were 6.5%. In addition, nonusers of PPIs were 89.5%, 14.6% had DM, 29.8% had hypertension, 14.3% had dyslipidemia, and 1.4% had polypectomy. Secondly, most of the participants belonging to "constantly low" were also women (55.5%), the percentage of those in their 60s and above was 24.4%, the percentage living in rural areas was 51.1%, and the percentage of participants with employee insurance was 56.4%. Most of the participants belonged to the upper-middle-income level (32.5%), the participants with CCI scores of 2 or more were 5.7%, and the percentage of nonusers of PPIs was 76.2%. 13.8% had DM, 29.2% had hypertension, 16.2% had dyslipidemia, and 2.2% had a history of polypectomy. Thereafter, most of the participants in the "Moderate to slightly decreased" group were men (51.9%), and the percentages of individuals aged 60 and above were 40.7%. Of these, 58.2% lived in rural areas, and 51.0% had employee insurance. The percentage of participants belonging to the upper-middle-income level was 30.8%, and those with a CCI score of 2 or more were

11.7%. The percentage of PPI nonusers was 67.3%, those with DM were 22.2%, those with hypertension were 47.3%, those with dyslipidemia were 26.2%, and those with polypectomy experience were 2.9%. Next, most of the participants belonging to “Low to sharply increased” were men (50.1%), 60 and above (47.5%), lived in rural areas (57.0%), and had employee insurance (53.9%). In addition, the percentage belonging to the upper-middle-income level was the highest (30.6%), and the percentage with a CCI of 2 or more was 9.8%. Also, among them, the percentage of nonusers of PPIs was the highest (74.9%), 22.2% had DM, 53.7% suffered from hypertension, 24.8% suffered from dyslipidemia, and 2.9% had underwent polypectomy. Participants belonging to “Constantly high” had the same percentage of males and females at 50%, and those in the age group 60 and above accounted for 62.5%. The percentage of participants living in rural areas was 57.6%, and those with employee insurance were 60.3%. 34.8% belonged to the upper-middle-income level, and 20.1% of participants with a CCI score of 2 or more. 77.7% were PPIs nonusers, 34.8% had DM, 65.2% had hypertension, 31.0% had dyslipidemia, and 1.6% had a history of polypectomy (Table 13).

To determine the difference in GI cancer incidence according to the trajectory groups, the Chi-squared test and Fisher's exact test were performed. The group with the most overall GI cancer was “Constantly high” (3.3%). When considering the subtypes, the group with the higher number of stomach cancer (1.6%) and colorectal cancer (1.6%) cases was also “Constantly high,” and the group with the highest number of liver cancer was “Low to sharply increased” (1.3%). The group with the most esophageal cancer cases was

"Constantly high" (0.5%), and the group with the most pancreatic cancer cases was "Moderate to slightly decreased" (0.6%). The cancer types that showed a statistically significant difference from the trajectory groups were overall GI cancer (p=0.046), liver cancer (p=0.001), and esophageal cancer (p=0.013) (Table 14).

Table 13. Sociodemographic characteristics of each trajectory group

Variables	Trajectory groups of DDD of ranitidine and/ or nizatidine exposure										*p**
	Nonuser		Constantly low		Moderate to slightly decreased		Low to sharply increased		Constantly high		
	(n=15,384)		(n=14,204)		(n=545)		(n=451)		(n=184)		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Sex†											0.001
Male	6,945	(45.1)	6,323	(44.5)	283	(51.9)	226	(50.1)	92	(50.0)	
Female	8,439	(54.9)	7,881	(55.5)	262	(48.1)	225	(49.9)	92	(50.0)	
Age†											<0.001
20~29	1,833	(11.9)	1,765	(12.4)	27	(5.0)	15	(3.3)	3	(1.6)	
30~39	2,963	(19.3)	2,859	(20.1)	60	(11.0)	40	(8.9)	8	(4.3)	
40~49	3,636	(23.6)	3,440	(24.2)	104	(19.1)	81	(18.0)	22	(12.0)	
50~59	2,937	(19.1)	2,668	(18.8)	132	(24.2)	101	(22.4)	36	(19.6)	
≥60	4,015	(26.1)	3,472	(24.4)	222	(40.7)	214	(47.5)	115	(62.5)	
Region†											0.001
Rural	7,935	(51.6)	7,259	(51.1)	317	(58.2)	257	(57.0)	106	(57.6)	
Urban	7,449	(48.4)	6,945	(48.9)	228	(41.8)	194	(43.0)	78	(42.4)	
Social security†											0.258
Medical aid	52	(0.3)	41	(0.3)	1	(0.2)	1	(0.2)	1	(0.5)	
Insurance (Regional)	6,703	(43.6)	6,150	(43.3)	266	(48.8)	207	(45.9)	72	(39.1)	
Insurance (Corporate)	8,629	(56.1)	8,013	(56.4)	278	(51.0)	243	(53.9)	111	(60.3)	
Income†											0.447
Low	2,340	(15.2)	2,130	(15.0)	80	(14.7)	83	(18.4)	35	(19.0)	
Lower middle	3,905	(25.4)	3,648	(25.7)	138	(25.3)	107	(23.7)	34	(18.5)	
Upper middle	4,987	(32.4)	4,611	(32.5)	168	(30.8)	138	(30.6)	64	(34.8)	
High	4,152	(27.0)	3,815	(26.9)	159	(29.2)	123	(27.3)	51	(27.7)	

(continued)

Table 13. Sociodemographic characteristics of each trajectory group (continued)

Variables	Trajectory groups of DDD of ranitidine and/ or nizatidine exposure										*p**
	Nonuser		Constantly low		Moderate to slightly decreased		Low to sharply increased		Constantly high		
	(n=15,384)		(n=14,204)		(n=545)		(n=451)		(n=184)		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
CCI†											<0.001
0	11,392	(74.1)	10,706	(75.4)	341	(62.6)	279	(61.9)	85	(46.2)	
1	2,997	(19.5)	2,684	(18.9)	140	(25.7)	128	(28.4)	62	(33.7)	
≥2	995	(6.5)	814	(5.7)	64	(11.7)	44	(9.8)	37	(20.1)	
Cumulative DDD of PPIs											<0.001
Nonusers	13,770	(89.5)	10,829	(76.2)	367	(67.3)	338	(74.9)	143	(77.7)	
<50 DDD	1,268	(8.2)	2,520	(17.7)	107	(19.6)	71	(15.7)	23	(12.5)	
50~99 DDD	229	(1.5)	596	(4.2)	43	(7.9)	21	(4.7)	11	(6.0)	
≥100 DDD	117	(0.8)	259	(1.8)	28	(5.1)	21	(4.7)	7	(3.8)	
Diabetes Mellitus											<0.001
No	13,132	(85.4)	12,249	(86.2)	424	(77.8)	351	(77.8)	120	(65.2)	
Yes	2,252	(14.6)	1,955	(13.8)	121	(22.2)	100	(22.2)	64	(34.8)	
Hypertension											<0.001
No	10,805	(70.2)	10,050	(70.8)	287	(52.7)	209	(46.3)	64	(34.8)	
Yes	4,579	(29.8)	4,154	(29.2)	258	(47.3)	242	(53.7)	120	(65.2)	
Dyslipidemia											<0.001
No	13,191	(85.7)	11,910	(83.8)	402	(73.8)	339	(75.2)	127	(69.0)	
Yes	2,193	(14.3)	2,294	(16.2)	143	(26.2)	112	(24.8)	57	(31.0)	
Polypectomy											<0.001
No	15,173	(98.6)	13,893	(97.8)	529	(97.1)	438	(97.1)	181	(98.4)	
Yes	211	(1.4)	311	(2.2)	16	(2.9)	13	(2.9)	3	(1.6)	

Abbreviation: CCI, Charlson comorbidity index; DDD, Defined daily dose; PPIS, Proton pump inhibitors; N/A, Not available
* p-value from Chi-squared test and Fisher's exact test
† Variables used for propensity score matching analysis

Table 14. GI cancer incidence depends on the trajectory groups

Cancer types	Trajectory groups of DDD of ranitidine and/ or nizatidine exposure										*p**
	Nonuser		Constantly low		Moderate to slightly decreased		Low to sharply increased		Constantly high		
	(n=15,384)		(n=14,204)		(n=545)		(n=451)		(n=184)		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Overall cancer											0.046
No	15,161	(98.6)	13,993	(98.5)	532	(97.6)	440	(97.6)	178	(96.7)	
Yes	223	(1.4)	211	(1.5)	13	(2.4)	11	(2.4)	6	(3.3)	
Gastric cancer											0.060
No	15,300	(99.5)	14,138	(99.5)	539	(98.9)	448	(99.3)	181	(98.4)	
Yes	84	(0.5)	66	(0.5)	6	(1.1)	3	(0.7)	3	(1.6)	
Colorectal cancer											0.258
No	15,304	(99.5)	14,137	(99.5)	543	(99.6)	449	(99.6)	181	(98.4)	
Yes	80	(0.5)	67	(0.5)	2	(0.4)	2	(0.4)	3	(1.6)	
Liver cancer											0.001
No	15,346	(99.8)	14,147	(99.6)	543	(99.6)	445	(98.7)	184	(100.0)	
Yes	38	(0.2)	57	(0.4)	2	(0.4)	6	(1.3)	N/A**		
Esophageal cancer											0.013
No	15,379	(100.0)	14,198	(100.0)	545	(100.0)	451	(100.0)	183	(99.5)	
Yes	5	(0.0)	6	(0.0)	N/A**		N/A**		1	(0.5)	
Pancreatic cancer											0.055
No	15,366	(99.9)	14,188	(99.9)	542	(99.4)	451	(100.0)	184	(100.0)	
Yes	18	(0.1)	16	(0.1)	3	(0.6)	N/A**		N/A**		

Abbreviation: CCI, Charlson comorbidity index; DDD, Defined daily dose; PPIS, Proton pump inhibitors; N/A, Not available
* p-value from Chi-squared test
† Variables used for propensity score matching analysis
** There was no observation

1.5 Results from survival analyses with trajectory groups

To find out whether there is a difference in the occurrence of GI cancer according to the trajectory groups, Kaplan-Meier survival analysis was performed. As a result, it was found that there was a significant difference in the risk of GI cancer occurrence between the trajectory groups (p=0.030) (Figure 12). Before performing the Cox regression analysis, log-log plot was checked to confirm the proportional hazards assumption. However, two or three groups among the trajectory groups showed a tangled graph (Figure S2).

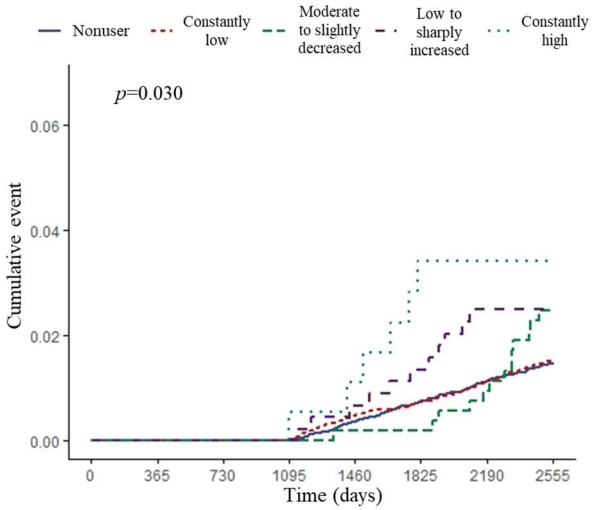

Figure 12. Kaplan-Meier survival curve with trajectory groups

The Cox regression analysis was performed to find out what kind of results were obtained when other sociodemographic variables were controlled. As a result, there was no significant result between trajectory groups and cancer incidence. However, the risk was

higher in the participants who were taking 50~99 DDD of PPIs (HR=1.66, 95% CI=1.08-2.53), and the participants with DM had a higher risk of developing GI cancer (HR=1.98, 95% CI=1.60-2.46). And, the participants with hypertension had a higher risk of cancer (HR=1.72, 95% CI=1.41-2.10). Lastly, the participants who experienced polypectomy had a higher risk of developing GI cancer (HR=1.69, 95% CI=1.02-2.78) (Table 15). The power of the analysis was 36.7%.

Table 15. Cox regression analyses with trajectory groups

Variables	Gastrointestinal cancer (n=30,768)	
	HR	**95% CI**
Ranitidine and/ or nizatidine		
Nonuser	1.00	
Constantly low	1.01	0.84 - 1.23
Moderate to slightly decreased	1.37	0.78 - 2.40
Low to sharply increased	1.39	0.76 - 2.56
Constantly high	1.69	0.75 - 3.81
Cumulative DDD of PPI		
Nonusers	1.00	
<50 DDD	0.96	0.73 - 1.28
50~99 DDD	1.66	1.08 - 2.53
≥100 DDD	1.23	0.63 - 2.40
Diabetes Mellitus		
No	1.00	
Yes	1.98	1.60 - 2.46
Hypertension		
No	1.00	
Yes	1.72	1.41 - 2.10
Dyslipidemia		
No	1.00	
Yes	0.95	0.75 - 1.20
Polypectomy		
No	1.00	
Yes	1.69	1.02 - 2.78

Abbreviation: HR, Hazard ratio; CI, Confidence interval; DDD, Daily defined dose; PPI, Proton pump inhibitor

Thereafter, subgroup analyses were performed according to the sex and age of the participants. The age groups were re-categorized into under 60s and over 60s. Firstly, as a result of analyses using the Kaplan-Meier method, it was found that there was a difference in the cancer risk in female according to the trajectory group (p=0.013) (Figure 13). In the case of age group, as a result of analyzing only participants under the age of 60 from 1 year of the landmark period, it was found that there was a significant difference in cancer risk according to the trajectory groups ($p < 0.001$) (Figure 14). With the results from Kaplan-Meier analysis, Cox regression analysis was performed on the subgroups. The "Moderate to slightly decreased" users (HR=2.29, 95% CI=1.11-4.76) who were women had a higher risk of GI cancer (Figure S3), and the power of the analyses were 39.2% in men and 10.5% in women. For the age groups, there was no significant association, and the power of the analyses were 29.5% in the participants who were below 60 years old and 11.0% in the participants above 60 years old.

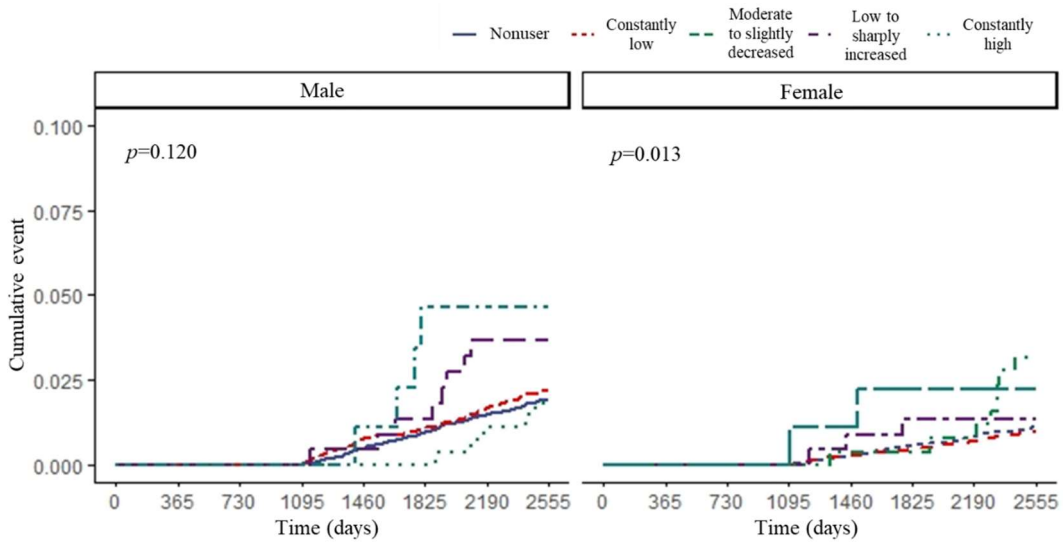

Figure 13. Subgroup analysis according to sex

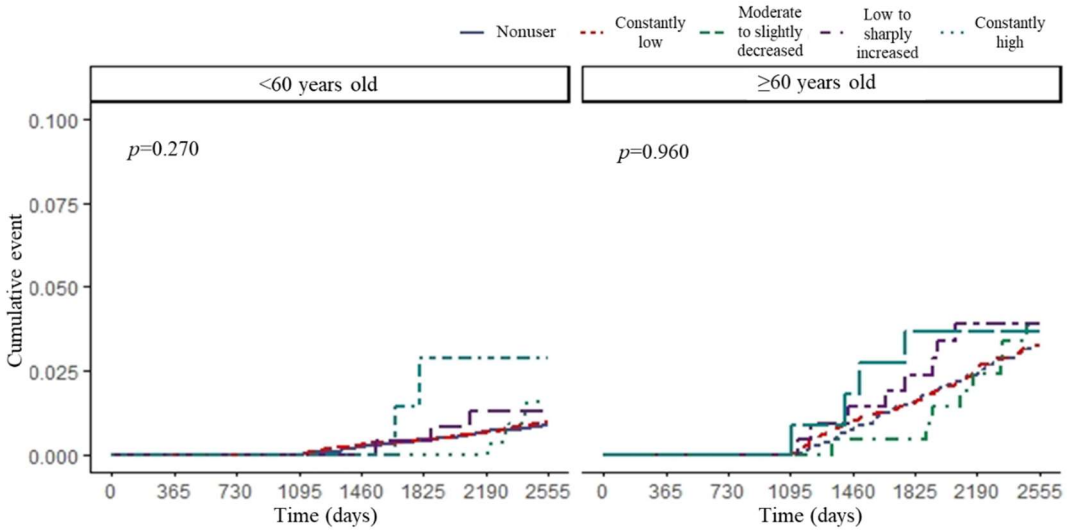

Figure 14. Subgroup analysis according to age

2. Nested case-control study with conditional logistic regression

2.1 Characteristics of the study participants

In the study design, participants who developed GI cancer were cases, and the participants who were at risk, but did not develop GI cancer were controls. Cases and controls were matched 1:5 by sex and age (sex: p=0.988, age: p=0.997). Exposure to ranitidine and nizatidine was observed from the time the participants first took H2RAs to 180 days before the onset of GI cancer. A period of 180 days was set because of the lag time between taking the drug to the onset of cancer. In addition, the cancer onset time of the controls was used as the date of the matched cases. A higher percentage of participants exposed to ranitidine and/or nizatidine was observed in the cases, but this was not statistically significant (cases=64.8%, controls=63.6%, p=0.694). As a result of calculating the exposure to these drugs as average prescription days per year, the percentage of participants who were exposed for more than 90 days was higher in cases (cases=5.4%, controls=4.1%, p=0.446). Considering the residence of the participants, the percentage living in urban areas was higher in controls (cases=44.5%, controls=45.6%, p=0.621). The percentage of participants with employee insurance was higher in controls (cases=62.5%, controls=64.2%, p=0.572), and the percentage of participants belonging to the high-income level was significantly higher in the controls (cases=31.7%, controls=33.0%, p=0.001). For the CCI score, the percentage of participants with 3 or more points was significantly higher in the cases (cases=49.8%, controls=12.2%, p<0.001). PPIs intake during exposure was

higher in cases (cases=37.9%, controls=30.3%, p=0.001). DM (cases=36.1%, controls=27.5%, p < 0.001), in addition to hypertension and dyslipidemia, were higher in the cases. Similarly, the history of polypectomy was also significantly higher in the cases (cases=13.4%, controls=5.6%, p<0.001) (Table 16).

Table 16. Sociodemographic characteristics of cases and controls

Variables	Gastrointestinal cancer				*p**
	Cases (n=634)		Controls (n=3,170)		
	n	(%)	n	(%)	
Ranitidine and/ or Nizatidine					0.694
Non-exposed	223	(35.2)	1144	(36.1)	
Exposed	411	(64.8)	2026	(63.9)	
Average prescription days					0.446
Nonuser	173	(27.3)	917	(28.9)	
<30 days/year	373	(58.8)	1,837	(57.9)	
30~90 days/year	54	(8.5)	286	(9.0)	
≥90 days/year	34	(5.4)	130	(4.1)	
Sex†					0.988
Male	388	(61.2)	1936	(61.1)	
Female	246	(38.8)	1234	(38.9)	
Age†					0.997
20~29	4	(0.6)	24	(0.8)	
30~39	13	(2.1)	61	(1.9)	
40~49	62	(9.8)	310	(9.8)	
50~59	126	(19.9)	630	(19.9)	
≥60	429	(67.7)	2145	(67.7)	
Region					0.621
Rural	352	(55.5)	1723	(54.4)	
Urban	282	(44.5)	1447	(45.6)	
Social security					0.572
Medical aid	12	(1.9)	70	(2.2)	
Insurance (Regional)	226	(35.6)	1066	(33.6)	
Insurance (Corporate)	396	(62.5)	2034	(64.2)	
Income					0.001
Low	71	(11.2)	537	(16.9)	
Lower middle	148	(23.3)	635	(20.0)	
Upper middle	214	(33.8)	952	(30.0)	
High	201	(31.7)	1046	(33.0)	

(continued)

Table 16. Sociodemographic characteristics of cases and controls (continued)

Variables	Gastrointestinal cancer				*p**
	Cases (n=634)		Controls (n=3,170)		
	n	(%)	n	(%)	
CCI					<0.001
0	126	(19.9)	1262	(39.8)	
1	84	(13.2)	1057	(33.3)	
2	108	(17.0)	465	(14.7)	
≥3	316	(49.8)	386	(12.2)	
Cumulative DDD of PPI					0.001
Nonusers	394	(62.1)	2211	(69.7)	
<50 DDD	157	(24.8)	583	(18.4)	
50~99 DDD	42	(6.6)	208	(6.6)	
≥100 DDD	41	(6.5)	168	(5.3)	
Diabetes Mellitus					<0.001
No	405	(63.9)	2298	(72.5)	
Yes	229	(36.1)	872	(27.5)	
Hypertension					0.353
No	291	(45.9)	1522	(48.0)	
Yes	343	(54.1)	1648	(52.0)	
Dyslipidemia					0.695
No	434	(68.5)	2198	(69.3)	
Yes	200	(31.5)	972	(30.7)	
Polypectomy					<0.001
No	549	(86.6)	2991	(94.4)	
Yes	85	(13.4)	179	(5.6)	

Abbreviation: CCI, Charlson comorbidity index; DDD, Defined daily dose; PPI, Proton pump inhibitor
* P-value from chi-squared test
† Variables used for propensity score matching analysis

There were cases in which two or more GI cancers were claimed on the same diagnosis date, and these were included in this study. Thus, there may be cancers that are counted as duplicates. 33.6% of the cases had stomach cancer, 33.0% had colorectal cancer, 23.0% had liver cancer, 2.8% had esophageal cancer, and 8.5% had pancreatic cancer (Table 17).

Table 17. Distribution of cancer types

Cancer types	Cases (n=634)	
	n	**(%)**
Gastric cancer		
No	421	(66.4)
Yes	213	(33.6)
Colorectal cancer		
No	425	(67.0)
Yes	209	(33.0)
Liver cancer		
No	488	(77.0)
Yes	146	(23.0)
Esophageal cancer		
No	616	(97.2)
Yes	18	(2.8)
Pancreatic cancer		
No	580	(91.5)
Yes	54	(8.5)

* There were some cases who had synchronous cancers (diagnosed with more than 1 gastrointestinal cancer type).

2.2 Result from conditional logistic regression

Firstly, as a result of analysis of exposure to ranitidine and/or nizatidine, there were no statistically significant results between the non-exposed and exposed groups. Variables that showed significant results in the analysis were income level, CCI, cumulative DDD of PPIs, presence of DM, dyslipidemia, and polypectomy. When the other covariates were controlled, lower-middle-income level (AOR=1.80, 95% CI=1.26-2.57), upper-middle income level (AOR=1.66, 95% CI=1.18-2.33), and high-income level (AOR=1.45, 95% CI=1.03-2.04) were significantly higher in the incidence of GI cancer. In addition, cancer incidence was significantly higher in CCI score 0 compared to 2 (AOR=2.78, 95% CI=2.07-3.74), and 3 or more (AOR=11.90, 95% CI=8.86-15.99). In addition, in the participants who underwent polypectomy, cancer incidence (AOR=2.20, 95% CI=1.59-3.04) was higher than in those who did not (Table 18). The power of the analysis was 8.1%.

Table 18. Conditional logistic regression with binary exposure

Variables	Gastrointestinal cancer (n=3,804)		*p*
	AOR	95% CI	
Ranitidine and/ or Nizatidine			
Non-exposed	1.00		
Exposed	0.95	(0.77 - 1.17)	0.615
Region			
Rural	1.00		
Urban	0.95	(0.78 - 1.15)	0.572
Social security			
Medical aid	1.00		
Insurance (Regional)	0.64	(0.31 - 1.34)	0.235
Insurance (Corporate)	0.68	(0.33 - 1.41)	0.295
Income			
Low	1.00		
Lower middle	1.80	(1.26 - 2.57)	0.001
Upper middle	1.66	(1.18 - 2.33)	0.004
High	1.45	(1.03 - 2.04)	0.033
CCI			
0	1.00		
1	0.91	(0.67 - 1.22)	0.518
2	2.78	(2.07 - 3.74)	<0.001
≥3	11.90	(8.86 - 15.99)	<0.001
Cumulative DDD of PPI			
Nonusers	1.00		
<50 DDD	1.33	(1.05 - 1.69)	0.020
50~99 DDD	0.97	(0.65 - 1.46)	0.890
≥100 DDD	0.94	(0.61 - 1.42)	0.752
Diabetes Mellitus			
No	1.00		
Yes	0.67	(0.53 - 0.85)	0.001
Hypertension			
No	1.00		
Yes	0.86	(0.69 - 1.06)	0.160
Dyslipidemia			
No	1.00		
Yes	0.79	(0.63 - 0.98)	0.033
Polypectomy			
No	1.00		
Yes	2.20	(1.59 - 3.04)	<0.001

Abbreviation: AOR, Adjusted odds ratio; CI, Confidence interval; CCI, Charlson comorbidity index; DDD, Defined daily dose; PPI, Proton pump inhibitor

2.3 Conditional logistic regression with average prescription days

Average prescription days per year was calculated using the total number of prescription days for ranitidine and/or nizatidine from the date of the first H2RAs intake to the date of cancer occurrence, minus the lag period. In addition, for the accuracy of the lag period, sensitivity analysis was performed with different periods. The lag time periods specified in this study were 180 days, 365 days, and 730 days. As a result of the analysis, statistically significant results were not obtained as in binary exposure. However, there significant results were obtained for income level, CCI score, presence of DM, dyslipidemia, and history of polypectomy. The variables showed that the longer the lag time period, the higher the AOR values. However, the cumulative DDD of PPIs became statistically insignificant considering the lag time. This is thought to be because the lag time was also considered when calculating the DDD of PPIs during the exposure period (Table 19). The powers of the analyses were 11.2% with 180 days, 13.0% with 365 days, and 5.7% with 730 days of lag time.

Following this, subgroup analysis was conducted according to sex and age, and each lag period was considered. In the case of age group, analyses were carried out by re-categorizing it into less than or greater than 60 years old. However, statistically significant results were not obtained in all lag periods (Figure S4, S5, S6).

Table 19. Conditional logistic regression with average prescription days per year

Variables	Lag time								
	180 days (n=3,804)		*p*	365 days (n=3,804)		*p*	730 days (n=3,804)		*p*
	AOR	95% CI		AOR	95% CI		AOR	95% CI	
Average prescription days									
Nonuser	1.00			1.00			1.00		
<30 days/year	0.95	(0.75- 1.19)	0.639	0.98	(0.78- 1.22)	0.823	0.95	(0.76- 1.19)	0.660
30~90 days/year	0.80	(0.55- 1.17)	0.247	0.75	(0.51- 1.10)	0.141	1.01	(0.71- 1.43)	0.968
≥90 days/year	0.86	(0.54- 1.38)	0.537	0.85	(0.52- 1.37)	0.501	0.89	(0.56- 1.41)	0.609
Region									
Rural	1.00			1.00			1.00		
Urban	0.94	(0.77- 1.14)	0.538	0.94	(0.77- 1.14)	0.525	0.95	(0.78- 1.15)	0.568
Social security									
Medical aid	1.00			1.00			1.00		
Insurance (Regional)	0.66	(0.32- 1.38)	0.267	0.66	(0.32- 1.37)	0.266	0.65	(0.31- 1.36)	0.253
Insurance (Corporate)	0.70	(0.34- 1.45)	0.337	0.70	(0.34- 1.46)	0.342	0.70	(0.34- 1.45)	0.334
Income									
Low	1.00			1.00			1.00		
Lower middle	1.79	(1.25- 2.56)	0.001	1.80	(1.26- 2.57)	0.001	1.80	(1.25- 2.57)	0.001
Upper middle	1.66	(1.18- 2.33)	0.004	1.66	(1.18- 2.34)	0.004	1.67	(1.19- 2.35)	0.003
High	1.44	(1.03- 2.03)	0.035	1.44	(1.02- 2.03)	0.036	1.45	(1.03- 2.03)	0.035
CCI									
0	1.00			1.00			1.00		
1	0.92	(0.69- 1.25)	0.602	0.92	(0.68- 1.24)	0.574	0.92	(0.68- 1.24)	0.571
2	2.85	(2.11- 3.83)	<0.001	2.84	(2.11- 3.82)	<0.001	2.85	(2.12- 3.84)	<0.001
≥3	12.28	(9.13- 16.51)	<0.001	12.39	(9.22- 16.65)	<0.001	12.23	(9.10- 16.44)	<0.001

(continued)

Table 19. Conditional logistic regression with average prescription days per year (continued)

Variables	Lag time								
	180 days (n=3,804)		*p*	365 days (n=3,804)		*p*	730 days (n=3,804)		*p*
	AOR	95% CI		AOR	95% CI		AOR	95% CI	
Cumulative DDD of PPI									
Nonusers	1.00			1.00			1.00		
<50 DDD	1.16	(0.90- 1.50)	0.252	1.12	(0.85- 1.46)	0.424	0.85	(0.63- 1.14)	0.275
50~99 DDD	0.96	(0.63- 1.46)	0.835	1.04	(0.68- 1.60)	0.857	0.86	(0.53- 1.41)	0.554
≥100 DDD	0.82	(0.52- 1.31)	0.413	0.59	(0.34- 1.05)	0.071	0.51	(0.25- 1.05)	0.067
Diabetes Mellitus									
No	1.00			1.00			1.00		
Yes	0.67	(0.53- 0.85)	0.001	0.68	(0.53- 0.86)	0.001	0.67	(0.53- 0.85)	0.001
Hypertension									
No	1.00			1.00			1.00		
Yes	0.86	(0.69- 1.06)	0.162	0.86	(0.69- 1.07)	0.176	0.85	(0.68- 1.05)	0.130
Dyslipidemia									
No	1.00			1.00			1.00		
Yes	0.79	(0.63- 0.99)	0.040	0.79	(0.63- 0.99)	0.042	0.80	(0.64- 1.00)	0.048
Polypectomy									
No	1.00			1.00			1.00		
Yes	2.22	(1.61- 3.07)	<0.001	2.24	(1.62- 3.10)	<0.001	2.28	(1.65- 3.15)	<0.001

Abbreviation: AOR, Adjuested odds ratio; CI, Confidence interval; CCI, Charlson comorbidity index; DDD, Defined daily dose; PPI, Proton pump inhibitor

* Region, Social security, Income, CCI, Cumulative DDD of PPI, Presence of diabetes mellitus, Presence of dyslipidemia, Presence of hypertention, History of polypectomy were also controlled.

IV. DISCUSSION

The results of the analysis of this study were similar to those from previous studies that used Korean health claimed data. There was no significant result between the incidence of cancer and exposure to ranitidine and/ or nizatidine (Kim et al., 2021; Yoon et al., 2021). In the risk-set matching study design, the hazard ratio was higher in the exposed group than in the non-exposed group; however, this result had no statistical significance and could be interpreted as a problem caused by low analysis power. The data used in this study showed that the proportion of patients who developed GI cancer was very small compared to those who took H2RAs. Therefore, it may affect the analysis power. In addition, the group that took a high dose in the trajectory groups were at a higher risk compared to the nonusers, and this is a study result that is comparable with the results of the U.S. FDA and previous lab experiments. The reason the results are different from the studies conducted as a retrospective study is because the definition of the participant is different and the amount of drug intake during the exposure period was analyzed by dividing it into trajectories according to the passage of time.

An interesting finding was that the colorectal cancer incidence was higher in the "Constantly high" users. This is consistent with the results analyzed using the FAERS data from the United States. The data used in this previous study contained information on adverse drug events, so it was possible to confirm the incidence of adverse digestive cancer after taking ranitidine. Among the cancers, colorectal cancer had the highest proportion (McGwin, 2021). This could be due to NDMA found in ranitidine and nizatidine. According

to a study conducted in Finland using follow-up data over 24 years, although there was no scientific evidence that NDMA causes cancer in other cancer types, it revealed that there was a strong association with colorectal cancer incidence (Knekt et al., 1999).

Secondly, the percentage of H2RAs users who were women was higher, but the risk of developing GI cancer was higher in men. In a study conducted in Taiwan, the proportion of GERD patients was statistically higher in women (Hung et al., 2011). Therefore, from the data of this study, the proportion of women was higher among patients suffering from gastric diseases, and thus it appears that H2RAs intake was also higher. A subgroup analysis was performed according to sex, wherein the risk of cancer was higher in men only when they took ranitidine and/or nizatidine compared to other H2RAs. This was a very meaningful result considering that sex is a very important index in pharmacokinetics and pharmacodynamics (Nicolas, Espie and Molimard, 2009). In an experimental study conducted using laboratory rats, when ranitidine was administered to the rats, there was a statistically significant improvement in bioavailability in male rats, but not in female rats (Afonso-Pereira et al., 2016). As a result, it was possible to replicate the results in this study through the biological mechanism of men or life patterns different from those of women.

Next, GI cancer incidence showed positive associations with DM and the history of polypectomy. A previous study conducted with American veterans also showed that the presence of DM increased the risk of GI cancer, especially pancreatic cancer (Jamal et al., 2009). In addition, there was a study that investigated the incidence of GI cancer among type 2 DM. It was conducted with a large population-based cohort in the UK. As the result

of the study, it showed that the incidences of liver, pancreatic and colon cancer were higher in the patients with type 2 DM (de Jong et al., 2018). As of 2019, the prevalence of DM was 9.3% worldwide, thus the result in this study was very meaningful (Saeedi et al., 2019). And for the polypectomy, there was a study that showed the higher gastric cancer risk in the participants who experienced endoscopy and upper gastrointestinal series screening than who never-screened (Choi et al., 2015). It was conducted in Korea using national cancer screening program data. Therefore, people who had more screenings or had polypectomy are more likely to detect GI cancer early, and may appear to have a higher risk of developing cancer.

The strength of this study is that the main interest variable was not simply negative or positive. The H2RAs intake of the participants was considered along with time and divided into trajectories, which enabled a more detailed analysis. Also, the average prescription days per year of the drugs was considered. However, since it is not cancer-specified data, the rate of GI cancer, an outcome variable, was not higher than the number of the study participants. Therefore, this study considered the five most frequently occurring GI cancers worldwide, which enabled a wider analysis. The second limitation was that the clinical and health examinations of the participants were not utilized. Smoking, drinking, eating habits, and BMI are risk factors that are closely related to GI cancer. The factors were not considered due to the characteristics of the sample cohort data with a very small number of health examination participants. To overcome this, during the exposure period, efforts were made to reduce the influence of variables that could not be considered by identifying

whether metabolic syndrome diseases. In addition, the DDD during the exposure period was calculated and considered in detail for taking PPIs, which increases the risk of GI disease when taken at high doses. The final limitation was that ranitidine and nizatidine are OTC drugs. The data used in this study was obtained from health insurance claims, and in the case of prescriptions not covered by insurance, it may not be recorded. That is, if a patient purchases ranitidine and nizatidine from a pharmacy without a doctor's prescription, the data may not be recorded. To reduce the misclassification of the participants with their exposure to ranitidine and nizatidine, the nested case-control study design was applied. By matching the control with the onset time of GI cancer of each case, exposure to ranitidine and nizatidine was randomly assigned. To an extent, this study design allowed to control for selection bias and immortal time bias.

V. CONCLUSION

This study investigated the association between ranitidine/ nizatidine and GI cancer incidence. The data used in this study was NHIS-NSC 1.0, and those who had never had cancer and had taken ranitidine and/or nizatidine for the first time in 2004, 2005, or 2006 were selected as participants for this study. And, two study designs were used to compare the results depending on the different settings. Firstly, the landmark analysis method, GBTM, and Cox proportional hazards model were used in the risk-set matching study design. Next, conditional logistic regression was used in the nested case-control study design.

As a result of the study, there was no significant association between the GI cancer risk and the exposure to ranitidine and/ or nizatidine in both study designs. However, it cannot be concluded that the use of ranitidine and nizatidine does not affect the GI cancer incidence. In future research, it is expected that more advanced results can be derived using cancer-specific data.

The carcinogenic impurities in ranitidine and nizatidine are still controversial. Accordingly, clinical trials, in-vitro tests, and retrospective studies are being actively conducted. As a result, there is a high possibility that novel results will be obtained. Based on the results of this as well as previous and future studies, the development of better and safer drugs must be emphasized.

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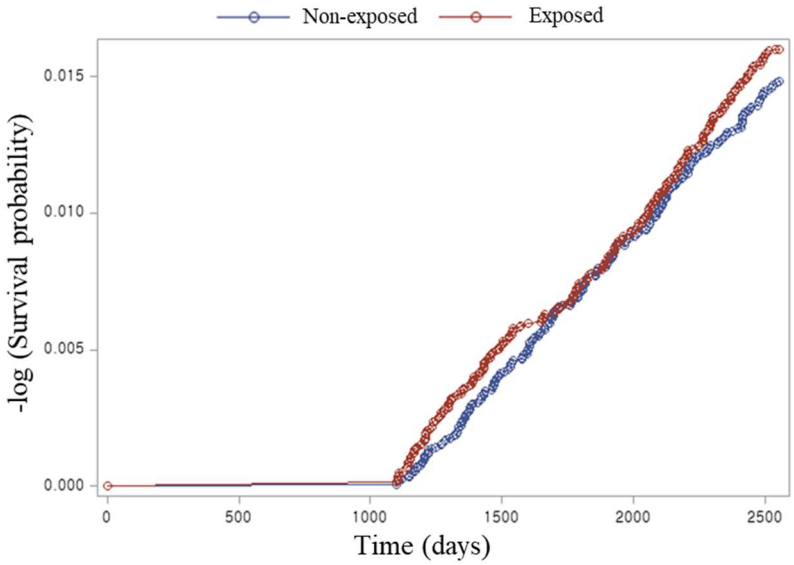
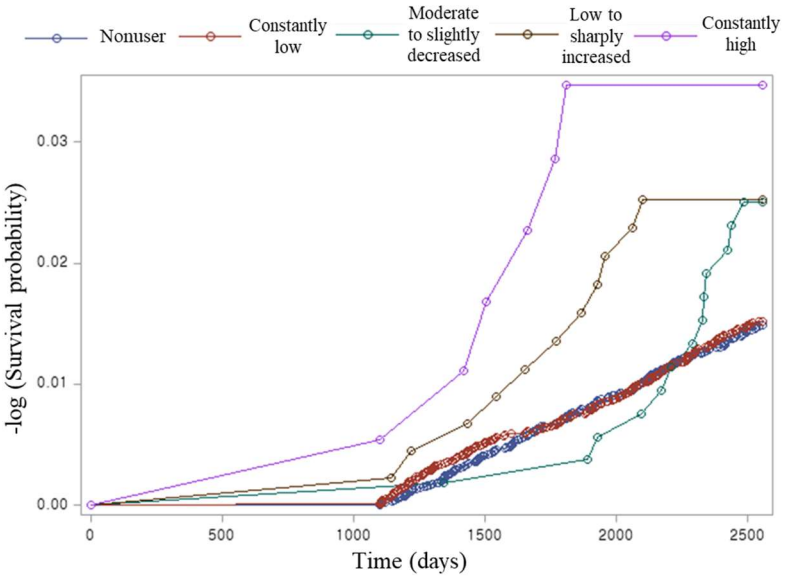
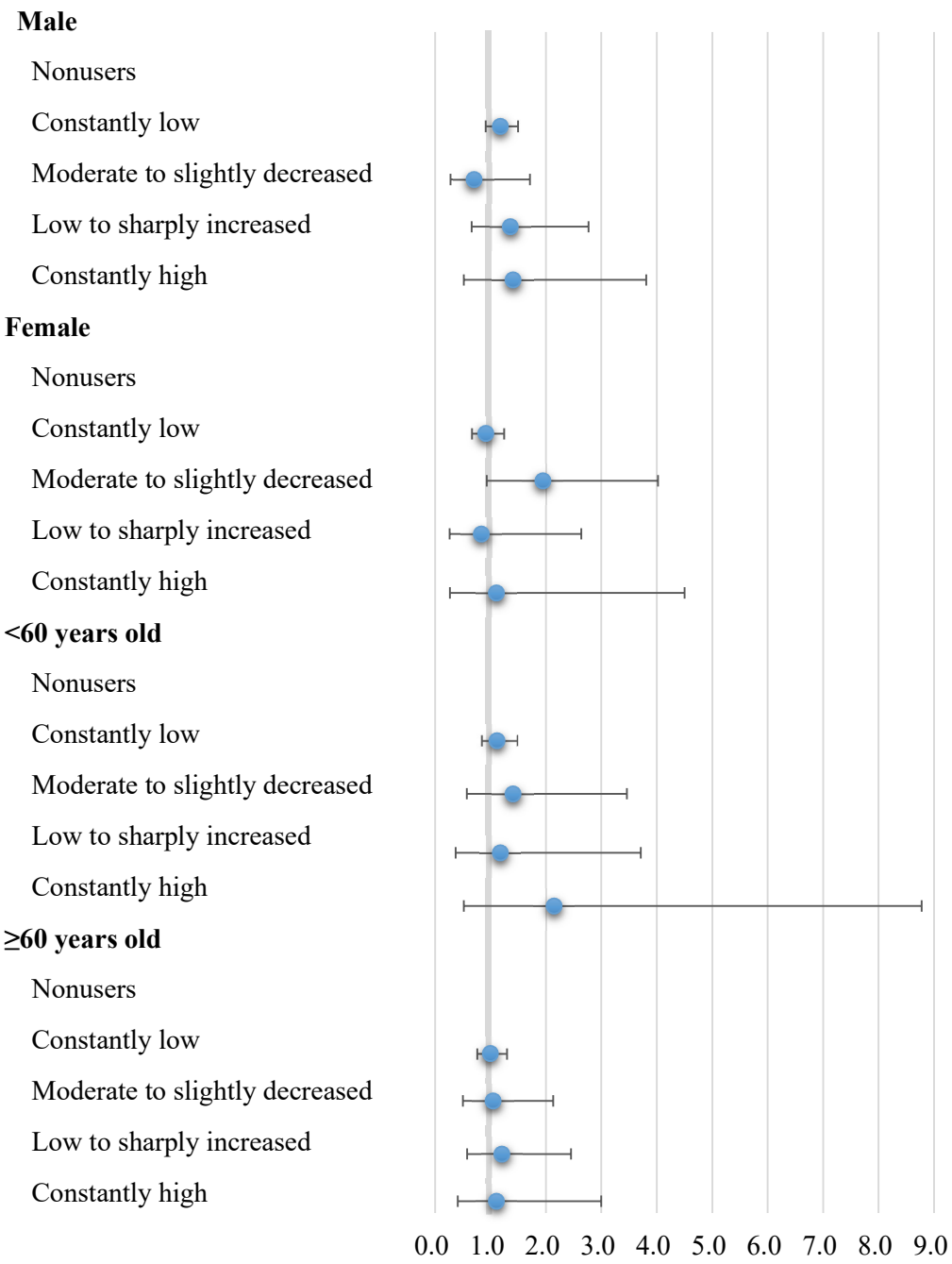
VII. APPENDIX



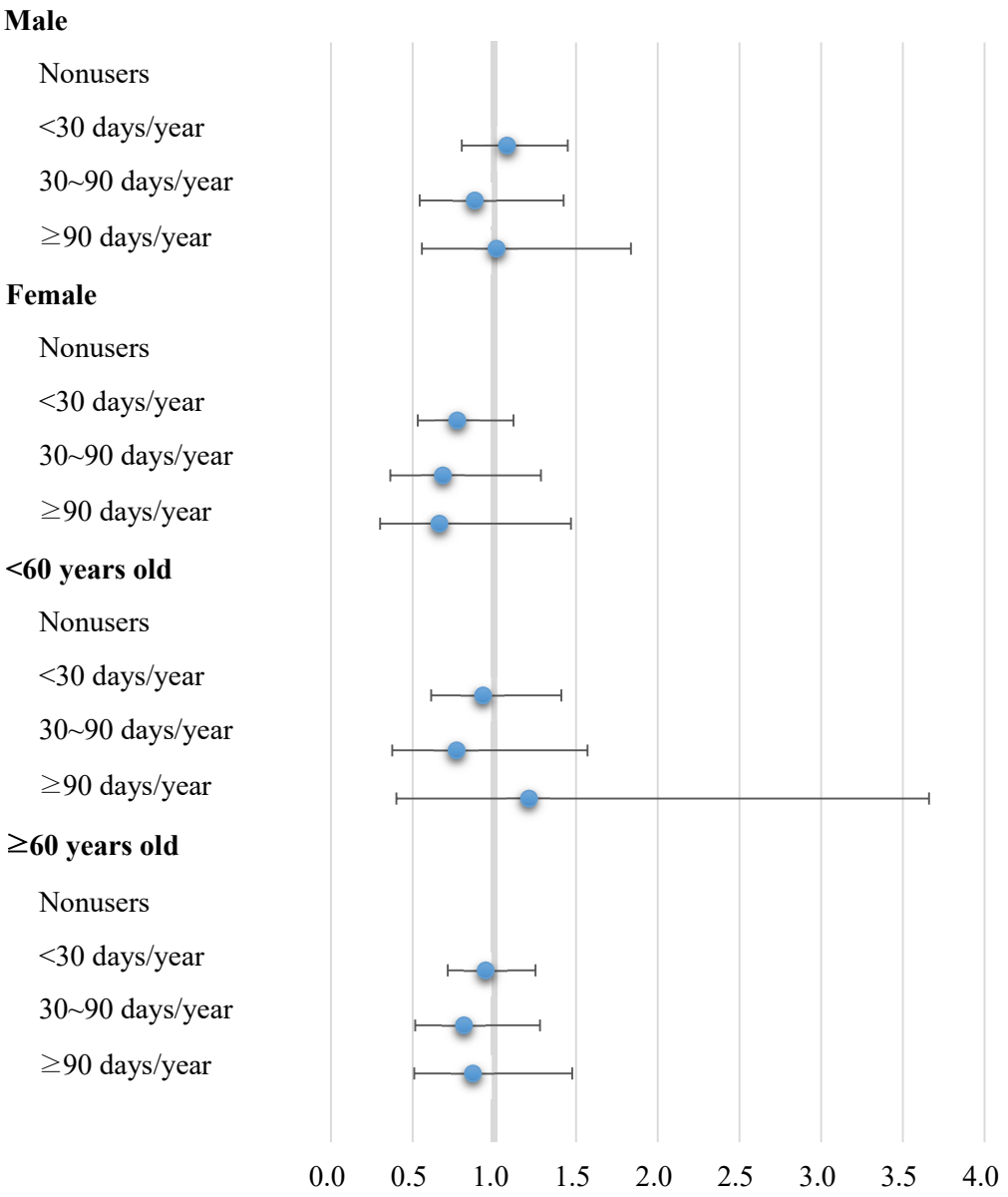
Supplemental figure S1. Log-log plot with binary exposure



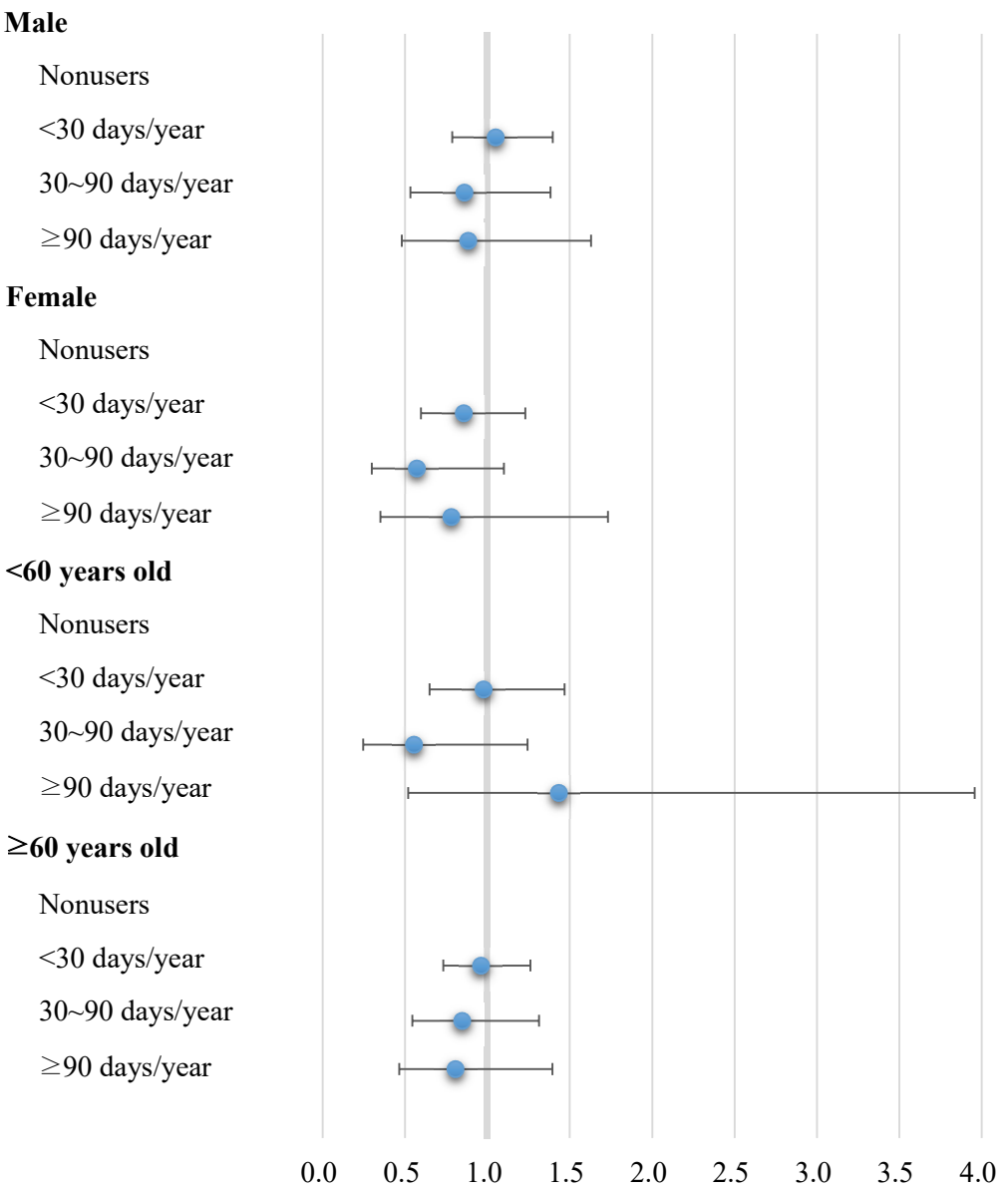
Supplemental figure S2. Log-log plot with trajectory groups



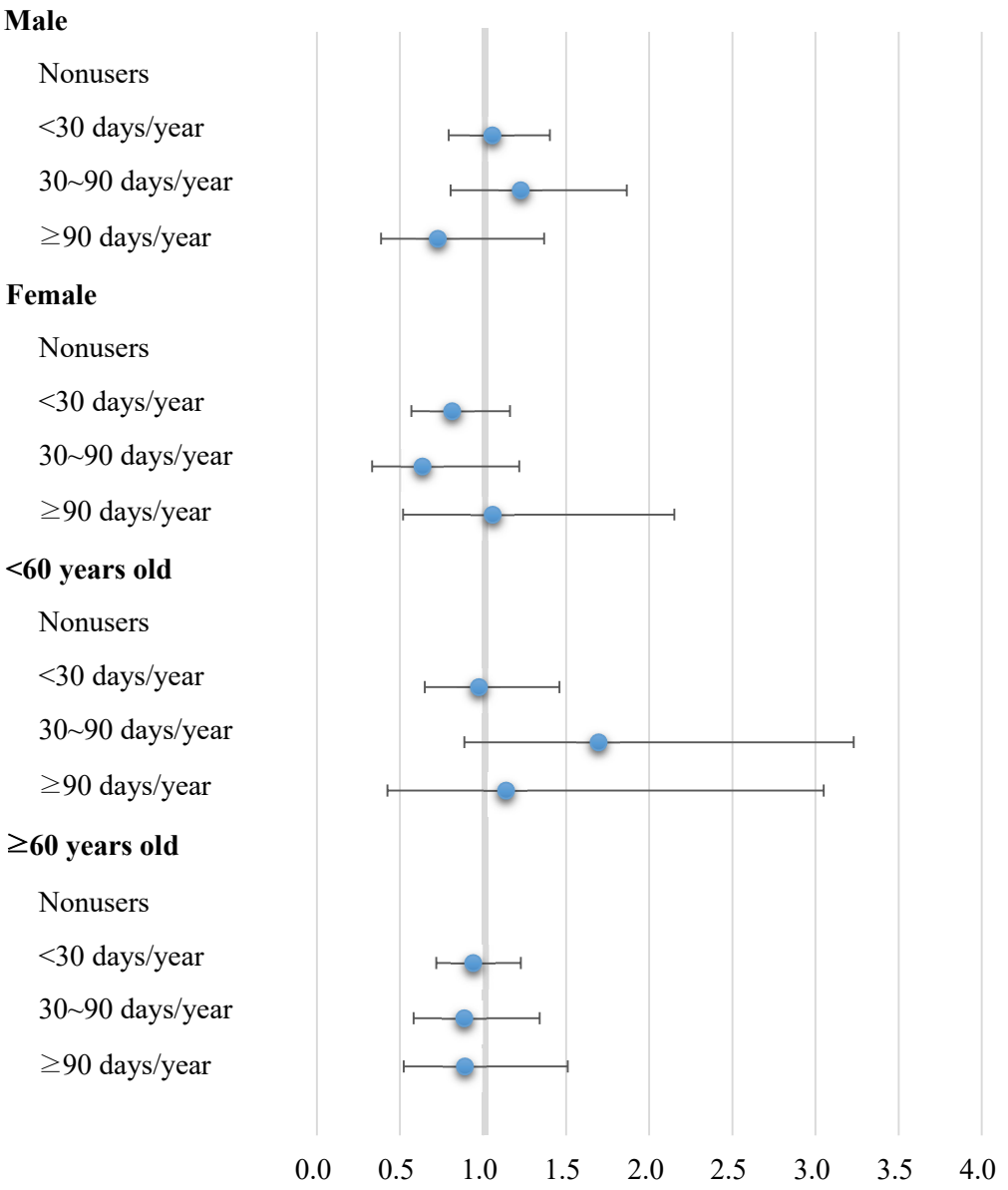
Supplemental figure S3. Results from the subgroup analyses



Supplemental figure S4. Results from the subgroup analyses (lag period: 180 days)



Supplemental figure S5. Results from the subgroup analyses (lag period: 365 days)



Supplemental figure S6. Results from the subgroup analyses (lag period: 730 days)

ABSTRACT (IN KOREAN)

라니티딘과 니자티딘의 복용이 소화기암 발생에 미치는 영향

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강혜정

연구 배경: 소화기암은 위, 대장, 간, 식도, 그리고 췌장 등과 같은 소화기 기관에 발생하는 암으로, 한국에서만 2020 년 한 해 동안 약 8,3034 건 정도가 발생하였다. 이는 김치나 장아찌와 같이 채소를 소금에 절여 먹는 한국인들의 식습관과 기름진 음식, 빈번한 폭음, 그리고 대사증후군 등이 영향을 준다고 알려져 있다. 좋지 못한 식습관과 스트레스 등은 인체에 역류성 식도염, 위궤양, 위염 등과 같은 질병들의 발생률을 높이고, 이는 소화기암으로 발전할 수 있다. 지난 2019 년, 미국의 FDA 에서는 소화기 질환 약물인 라니티딘(Ranitidine)과 니자티딘(Nizatidine)에 발암물질이 함유되어 있다는 실험 결과를 밝혔다. 이는 N-nitrosodimethylamine 이라고 알려진 물질로, 공업 현장에서 주로 사용된다. 하지만, 이후 진행된 연구들에선, 라니티딘 또는 니자티딘이 암 발생의 위험을 높인다는 연구 결과를 도출해내지

못하였다. 이에 따라, 본 연구에선 한국의 후향적 코호트 데이터를 사용하여, 한국 성인에게서 라니티딘과 니자티딘의 섭취가 소화기암 발생에 어떠한 영향을 미치는지 알아보고자 한다.

연구 방법: 본 연구에서 사용한 자료는 국민건강보험공단의 표본 코호트로, 건강보험에 가입된 대한민국 국민의 약 2% 정도를 추출하여 구축한 후향적 자료이다. 표본 데이터에서 2002 년에서 2004 년 사이에 사망하지 않았고, 암 경력이 없으며, 항히스타민 수용체 차단제(H2RAs)가 청구된 적이 없는 사람들을 대상으로, 3 년간의 랜드마크 기간(Landmark period) 동안 누적 복용일수가 30 일 이상인 대상자들을 1:1 성향점수매칭(Propensity score mathicng)시켰다. 이때, 노출 군은 노출 기간 동안 라니티딘과 니자티딘을 한 번이라도 처방 받은 적이 있는 사람이며, 비노출 군은 해당 약물들을 처방받은 적이 없는 사람들이었다. 이후, 랜드마크 기간 동안 라니티딘과 니자티딘의 평균 유지 용량(DDD, Defined daily dose)를 계산하여, 궤적 분석(Trajectory analysis)을 통해 궤적 그룹을 나누었고, 해당 그룹들을 사용해 콕스 회귀분석(Cox proportional hazard regression analysis)을 시행하였다. 두 번째로, 소화기암이 발생한 대상자를 환자군으로 정의하고, 같은 시점에 암 발생 위험에 놓여 있었으나 결과적으로 암이 발생하지 않았던 사람들을 대조군으로 하여, 환자군의 암이 진단 시점의 성별, 연령으로 성향점수 매칭을 1:5 비율로 시행하였다. 이후, 조건부 로지스틱 회귀 분석 방법(Conditional logistic regression analysis)을 사용하여 분석을 진행하였다.

연구 결과: 노출 매칭 환자-대조군 연구 디자인(Risk-set matching study design)으로 궤적 그룹을 나눠 콕스 회귀분석을 시행하였던 결과와 코호트 내 환자-대조군 연구 디자인(Nested case-control study design)으로 조건부

로지스틱 회귀분석을 시행하였던 결과 모두 통계적으로 유의한 결과를 얻지 못하였다. 이는 대상자들의 수에 비해 소화기암 발생 비율이 현저히 낮아 발생한 결과로 생각된다. 추가로 진행한 하위그룹 분석 결과, 여성에서 약물을 복용하지 않았던 군(Nonusers) 대비 중간 용량에서 서서히 용량을 줄여갔던 군(Moderate to slightly decreased)이 소화기암 발생 위험이 더 높은 것으로 나타났다 (HR=2.29, 95% CI=1.11-4.76).

연구 결론: 본 연구는 이전에 진행되었던 연구들과 달리, 여러 연구 디자인들과 분석 방법들을 사용하여 편향된 결과를 최소화하려고 노력하였다. 하지만, 자료의 특성상 암 환자에 대한 정보가 적어, 연구 결과를 도출하는데 한계점이 있었다. 더불어, 라니티딘과 니자티딘은 처방전 없이도 약국에서 구입할 수 있는 OTC(over-the-counter) 약물로, 청구 자료에서 고려하지 못한 투약 기록이 있을 수 있다. 추후 연구에선, 대상자들의 임상적 변수들과 검진 자료, 더불어 암 등록 자료를 활용하여 좀 더 발전된 연구 결과를 도출할 수 있을 것이다.

핵심 되는 말: 소화기암, 라니티딘, 니자티딘, 궤적 분석, 랜드마크 분석, 콕스 비례위험모형, 코호트 내 환자-대조군 연구, 조건부 로지스틱 회귀 분석