약학석사 학위논문

Nitrates와 국내 다빈도 암진단과의 연관성 조사

Cross Sectional Evaluation of the Relationship Between Nitrates and Cancer Diagnoses

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ABSTRACT

Cross Sectional Evaluation of the Relationship Between Nitrates and Cancer Diagnoses

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Background: To date, a number of pre-clinical and clinical studies have been conducted to examine the potential therapeutic effect of nitrates or nitric oxide in cancer prevention and treatment. However, the literature review showed contradictive findings. Since there is a lack of epidemiological studies examining the relations between nitrates and cancers, we conducted a study with an objective to explore the association between nitrates and cancer by using big-data. This study evaluated the association in the top five cancers in Korea, such as thyroid, stomach, colorectal, lung, and breast cancer using Korean national health claims sample data obtained from the Health Insurance Review and Assessment Service (HIRA) from 2010 to 2014.

Methods: A cross-sectional analysis of the nitrates use and cancer diagnoses was performed using the HIRA-NPS data from 2010 to 2014. Patients aged 19 years and older with at least one prescription claim for systemic nitrate product were included. Logistic regression analysis was used to evaluate multivariate associations between nitrates use and cancer diagnoses while adjusting confounding variables like gender, age, insurance type, obesity, smoking, and angina.

Results: From HIRA-NPS 2010-2014, 184,075,489(weighted) patients aged 19 years and older were identified. Patients with at least one prescription claim for systemic nitrate product were 0.79% (n=1,445,227, RSE, 0.476) of the total study population, and the total patient number with at least one neoplasm diagnosis of the top 5 cancers was 8,736,862 (4.7% of the total study population). Overall, nitrates users were more likely to be recorded with have neoplasm diagnoses. However, ISMN and ISDN users were about 50% (Adjusted OR, 0.532; 95% CI, 0.319- 0.886) and 20% (Adjusted OR, 0.792; 95% CI, 0.634-0.990), respectively, reduced likelihood to be diagnosed with benign neoplasm of thyroid gland.

Conclusions: The results of our study showed that the nitrate users were more likely to have cancer diagnoses, except benign neoplasm of thyroid gland. However, due to several limitations of this study, findings should be confirmed in further research examining the links between nitrates and the cancers.

Keywords: nitrates, cancer, cross sectional study, drug repurposing, HIRA

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1. INTRODUCTION

Cancer is a major cause of escalating mortality and morbidity worldwide. The incidence of cancer-related deaths was 8.2 million in 2012 with the expected rise in cancer cases by 70% over the next two decades [1]. Of all cancer deaths, the majority were caused by lung cancer in men and breast cancer in women, accounting for 30% and 12.9%, respectively [2].

In Korea, the five most common cancers were thyroid, stomach, colorectal (colon and rectum), lung, and breast cancer in 2012 (listed in order of highest incidence). Nearly two-third of all cancer incidences were from these cancer sites [3]. The highest mortality rate in men and women was caused by lung cancer in 2013, accounting for 22.8% of all cancer deaths [4].

Cancer causes not only health-related problems but also it has economic impacts by imposing a significant financial burden on cancer patients, their families, and to the society. The treatment of cancer is lengthy and exceedingly costly. One of the underlying causes of the high medical cost comes from anti-cancer drugs. As a strategy to overcome this issue, drug repurposing (or drug repositioning), the re-investigation of existing drugs for a new indication [5], has been studied. Drugs used in repurposing are mostly well-known and well-characterized pharmaceutical agents, and thus, a wealth of data on safety and toxicity profiles are available. Therefore, bypassing some of the early stages in *De novo* development

pathway, drug repurposing enables drug development time and cost saving [6].

Nitrates (such as nitroglycerin (NTG), isosorbide mononitrate (ISMN), and isosorbide dinitrate (ISDN)) are nitric oxide (NO) donor drugs that are originally discovered as a vasodilator [7, 8]. In recent studies, nitrates were shown to have anti-cancer properties through multiple mechanisms of action: pro-apoptotic effects, immunomodulation, anti-hypoxic activity, and vasodilation that lead the enhanced permeability and retention (EPR) effect of anticancer drugs. With respect to the anti-cancer effect, NO demonstrates biphasic properties. At lower concentrations (< 100nM), NO elicits pro-tumor effects of pro-angiogenesis, pro-proliferation, and anti-apoptosis. Whereas at higher NO concentrations (> 500 nM), NO elicits anti-tumor effects of cytotoxicity and pro-apoptosis [8, 9]. Due to possible antitumor effects of nitrates, NTG, one of the nitrates, is suggested as a candidate drug for repurposing by the Repurposing Drugs in Oncology (ReDO) project that is supported by researchers and clinicians from the Harvard University and non-profit organizations [8, 10].

To date, a number of pre-clinical and clinical trials examining the influence of nitrates or NO on cancer have been conducted, but the results are contradictive. A randomized phase II trial conducted in Japan against non-small-cell lung cancer (NSCLC) patients showed that the concurrent use of NTG and chemotherapy increased the overall response rate, time to progression, and overall survival compared to the group without

NTG [11]. In the subsequent replicated-phase II trial conducted in Germany, although the results were not statistically significant, the chemotherapy with NTG group showed higher overall response rate and the disease control rate than the chemotherapy-only group [12]. These positive outcomes were not limited to the lung cancer patients. The combination therapy with NTG showed positive clinical outcomes in patients with prostate cancer by doubling PSA time and those with liver cancer by reducing tumor diameter [13, 14]. These results from previous studies support a clinical role, although pleiotropic, of nitrates or NO in the treatment of cancer. However, other clinical studies conducted in Netherlands, Australia, and Korea showed that the addition of nitrates to chemotherapy did not improved the outcomes such as response rate or survival [15-17].

Although several studies have been conducted to examine the potential therapeutic effect of nitrates or NO in cancer treatment and prevention, the findings are still contradictive. Since there is a lack of epidemiological studies examining the relations between nitrates and cancers, we conducted a study with an objective to explore the association between nitrates and cancer by using big-data. Our study was designed to evaluate cross-sectional association between nitrates prescriptions and diagnoses with the top five cancers in Korea, such as thyroid, stomach, colorectal, lung, and breast cancer using Korean national health claims sample data obtained from the Health Insurance Review and Assessment Service (HIRA) from 2010 to

2014.

2. MATERIALS & METHODS

2.1 Data Source: HIRA-NPS data.

This cross-sectional, population-based study used the sample datasets provided by HIRA called the National Patients Samples of the Health Insurance Review and Assessment Service (HIRA-NPS) [18].

In Korea, about 97.0% of the total population is enrolled in the Korean National Health Insurance (NHI) Program, and the claims from NHI program are reviewed by HIRA. Although the remaining 3% is not insured by the Korean NHI program, clinics and hospitals have to submit claims to HIRA for each service provided to get reimbursement, regardless of the patients' enrollment status in the NHI program. Thus, technically almost all medical claims with patient information and medical records in Korea are available from the HIRA database [19].

The HIRA-NPS is a dataset of the stratified sample data from the HIRA database reflecting the health insurance data of the entire national population of approximately 50 million beneficiaries [20, 21]. Each HIRA-NPS data provides approximately 1.4 million patients' one-year-medical record (with a sampling rate of 3%). These sample data contain de-identified patient information and medical records: age, gender, diagnosis, date of hospital visits, drug prescriptions received during inpatient and outpatient visits, hospital admission, medical procedures, and drug related information [21].

In this study, the datasets of HIRA-NPS 2010 (Serial

number: HIRA-NPS-2010-0084), HIRA-NPS 2011 (Serial number: HIRA-NPS-2011-0110), HIRA-NPS 2012 (Serial number: HIRA-NPS-2012-0069), HIRA-NPS 2013 (Serial number: HIRA-NPS-2013-0078), and HIRA-NPS 2014 (Serial number: HIRA-NPS-2014-0054) were used.

2.2 Study Population

The nitrates user group was defined as those who (1) aged 19 years and older, (2) with at least one prescription claim for systemic nitrate product. A patient record with one or more cancer diagnoses were defined as the patient with the specific cancer in the HIRA-NPS datasets between January 2010 and December 2014.

The patient population was classified into five age groups: 19-34 years, 35-49 years, 50-64 years, 65-79 years and 80 years and older groups. Other patient demographic characteristics such as gender and insurance type were also collected.

2.2.1 Definition of Nitrates User

The Korea Pharmaceutical Information Center (KPIC) classified NTG, ISMN, ISDN, eritrityl tetranitrate, propatylnitrate, tenitramine, and trolnitrate as nitrates. Of the seven nitrate drugs, only the generic medications that were available in Korea were included in this study: NTG, ISMN, and ISDN.

The NTG ointments for hemorrhoids were excluded, because they were not included in the formulary of the NHI;

they were out-of-pocket medications.

The nitrate drug codes that were used in this study were listed in Table 1.

Drug codes were extracted from a variable "GNL_NM_CD" or "GNL_NM_CD_8" of Table 30 of HIRA data which contains specific information on health care services provided [22].

Table 1. Nitrate Drug Codes

Drug	NTG	ISMN	ISDN
Drug Code	202501BI, 202505BI, 202507BI, 202604CS, 202504CP, 202602AT	178501AT, 178502AT, 178504AT, 178505AT, 178502AC, 178503AC	178403AC, 178406AC, 178407AC, 178407AT, 178401AT, 178407AT, 178405CS, 178401BI, 178404BI

2.2.2 Definition of Cancer Diagnoses

The incidence of cancer diagnosis was identified using the Korean Standard Classification of Diseases 6threvision (KCD-6) code which was developed on the basis of the International Classification of Diseases 10threvision (ICD-10) by the World Health Organization (WHO) [20].

Of the KCD-6 codes for neoplasms (C00-D48), codes for thyroid, stomach, colon and rectum, lung, and breast were sorted out. Then, each cancer type was categorized into malignant neoplasm, carcinoma *in situ*, benign neoplasm, and neoplasm of uncertain or unknown behavior.

The KCD-6 codes for the lung were malignant neoplasm (C34, C34.X, C34.XX), carcinoma *in situ* (D02.2, D02.2X), benign neoplasm (D14.3, D14.3X), and neoplasm of uncertain or unknown behavior (D38.1). For the neoplasm of stomach, the codes of malignant neoplasm (C16, C16.X, C16.XX), carcinoma *in situ* (D00, D00.2), benign neoplasm (D13.1), and neoplasm of uncertain or unknown behavior (D37.1) were used. For the neoplasm of breast, the codes of malignant neoplasm (C50, C50.X, C50.XX), carcinoma *in situ* (D05, D05.X, D05.XX), benign neoplasm (D24, D24.0, D24.0X), and neoplasm of uncertain or unknown behavior (D48.6, D48.6X) were used. For the neoplasm of thyroid gland, the codes of malignant neoplasm (C73), carcinoma *in situ* (D09.3), benign neoplasm (D34), and neoplasm of uncertain or unknown behavior (D44.0) were used. The colorectal cancer was defined according to the International Classification of Disease 10th revision (ICD-10) codes from C18-C21[23] and disease classification by the Korean National

Cancer Center[24]; and, the codes of malignant neoplasm (C18, C18.X, C19, C20), carcinoma *in situ* (D01.0, D01.1, D01.2), benign neoplasm (D12, D12.0, D12.1, D12.2, D12.3, D12.4, D12.5, D12.6, D12.7, D12.8), and neoplasm of uncertain or unknown behavior (D37.4, D37.5) were used (Table 2).

Disease codes were extracted from a variable "MSICK_CD" (major diagnosis) or "SSICK_CD" (secondary diagnosis) of Table 20 of HIRA data which contains general characteristics of the patient [22]. Only single code for each "MSICK_CD" or "SSICK_CD" was available per claim. Since HIRA data contain records for one year, patients could have multiple claims, and thus, some patients had multiple codes for "MSICK_CD" or "SSICK_CD".

A table for diagnostic information (Table 40) [22] of HIRA data which can provide more than two diagnosis codes per claim was not used due to missing information when connecting Table 20, a main table, with Table 40 by table joint key.

Table 2. Disease Codes (KCD-6) of the Top Five Cancers in Korea

	Thyroid	Stomach	Colon and Rectum	Lung	Breast
Malignant Neoplasm	C73	C16, C16.X, C16.XX	C18, C18.X, C19, C20	C34, C34.X, C34.XX	C50, C50.X, C50.XX
Carcinoma *in situ*	D09.3	D00, D00.2	D01.0, D01.1, D01.2	D02.2, D02.2X	D05, D05.X, D05.XX
Benign Neoplasm	D34	D13.1	D12, D12.0, D12.1, D12.2, D12.3, D12.4, D12.5, D12.6, D12.7, D12.8	D14.3, D14.3X	D24, D24.0, D24.0X
Neoplasm of uncertain or unknown behavior	D44.0	D37.1	D37.4, D37.5	D38.1	D48.6, D48.6X

2.2.3 Definition of Confounding Variables: Smoking, Obesity, and Angina

Smoking and obesity are confounding variables of cancers. However, as drugs for smoking cessation or weight reduction were not included in the formulary of the NHI, they could not be used as proxy indicators of the smoking and obesity status. Instead, disease codes of obesity (E66, E66.X) and mental and behavioral disorders due to the use of tobacco (F17, F17.X) or the toxic effect of tobacco and nicotine (T65.2) were used (Table3).

Angina was considered as a confounding variable, because it is a main approved indication for the nitrates and it was neither inclusion nor exclusion criterion of the study population of previous studies. The KCD-6 codes of unstable angina, prinzmetal angina, other forms of angina pectoris, and unspecified angina pectoris (I20, I20.X, I20.XX) were used (Table 3).

Disease codes were extracted from a variable "MSICK_CD" or "SSICK_CD" of Table 20 of HIRA data [22].

Table 3. Disease codes (KCD-6) for disease related confounders

Disease	Obesity	Smoking	Angina
Disease Codes	E66, E66.X	F17, F17.X, T65.2	I20, I20.X, I20.XX

2.3 Statistical Analysis

All analyses in the study aimed to yield national level estimates reflecting all Korean insurance coverage using weighting procedures. Each visit record is assigned a weight variable called the "sampling weight" provided by HIRA which is a statistical weight for inflating the sample data to reflect the national level estimates. Unweighted analyses were also performed. Descriptive statistics were used to evaluate the demographic characteristics of the study population. The categorical variables (gender, age group, public insurance scheme) were reported as number (with 95% confidence interval [CI]) and proportions (percentages and relative standard error [RSE]). Continuous variables were summarized in means and standard deviations. Multivariate associations between nitrates use and cancer diagnoses were evaluated performing logistic regression analysis while adjusting confounding variables like gender, age, insurance type, obesity, smoking, and angina. The results from logistic regression analyses were reported as odds ratio (OR) with 95% CI.

Prescribed drug records or diagnosed disease records were not mutually exclusive, meaning a patient may be prescribed more than one type of nitrate product or have one or more cancer diagnoses in one year. Thus, the number of patients with all nitrates prescription or top 5 cancer diagnoses may exceed the sum of each nitrate prescription or cancer diagnoses.

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

2.4 Ethics Statement

This study was approved by the Seoul National University Institutional Review Board (IRB) (Approval Number: IRB No. E1511/002-001).

3. RESULTS

3.1 Demographic Characteristics of all adult patients

From HIRA-NPS 2010-2014, 184,075,489(weighted) patients aged 19 years and older were identified. Of those, males and females comprised 47.45% (RSE, 0.000) and 52.55% (RSE, 0.000), respectively, of the total study population. The mean age of the 184,075,489 patients was 46.6 years (SD, 17.73). Patients aged 35-49 years group (31.11%; RSE, 0.020) comprised the largest portion, followed by 19-34 years group (27.26%; RSE, 0.015) and 50-64 years group (25.60%; RSE, 0.023). In addition, most patients were NHI (96.62%; RSE, 0.008) insured, and about 3% of the total patients were under Medicaid (3.28%; RSE, 0.229) or veterans' healthcare (0.10%; RSE, 1.329). Patients with at least one obesity, smoking, and angina diagnosis were 0.07% (RSE, 1.556), 0.01% (RSE, 4.360), and 2.42% (RSE, 0.266), respectively (Table 4).

Table 4. Demographic characteristics of the study population

	Unweighted Number of patients	Weighted Number of patients (95% CI)	Weighted % (RSE%)
Overall population visits	5,521,735	184,075,489	100
Gender			
Female	2,901,654	96,730,634 (96,730,381 -96,730,933)	52.55 (0.000)
Male	2,620,081	87,344,854 (87,344,556 -87,345,108)	47.45 (0.000)
Age group			
19-34	1,506,283	50,172,443 (50,157,626-50,187,262)	27.26 (0.015)
35-49	1,718,162	57,264,649 (57,242,139-57,287,053)	31.11 (0.020)
50-64	1,413,010	47,114,378 (47,092,953-47,135,842)	25.60 (0.023)
65-79	717,464	23,936,137 (23,913,615-23,958,713)	13.00 (0.048)
80 and older	166,816	5,587,882 (5,569,756-5,606,019)	3.04 (0.166)
Insurance Scheme			
Health insurance	5,335,371	177,857,766 (177,830,360-177,885,214)	96.62 (0.008)
Medicaid	180,757	6,030,644 (6,003,622-6,057,740)	3.28 (0.229)
Veteran healthcare	5,607	187,079 (182,235-191,991)	0.10 (1.329)
Obesity	4,128	137,561 (133,455-141,738)	0.07 (1.556)
Smoking	526	17,533 (16,015-18,960)	0.01 (4.360)
Angina	133,297	4,447,560 (4,424,438-4,470,641)	2.42 (0.266)
Nitrates	43,310	1,445,227 (1,431,739-1,458,798)	0.79 (0.476)
NTG	34,911	1,164,796 (1,152,681-1,176,979)	0.63 (0.532)
ISMN	4,472	149,310 (144,867-153,703)	0.08 (1.494)
ISDN	15,202	507,411 (499,397-515,411)	0.28 (0.808)

(Table 4 Continued)

Lung			
Malignant	10,594	353,623 (346,982-360,420)	0.19 (0.968)
In Situ	93	3,110 (2,393-3,682)	0.00 (10.369)
Benign	5,143	171,537 (166,772-176,160)	0.09 (1.393)
Unknown	1,809	60,352 (57,616-63,138)	0.03 (2.351)
Stomach			
Malignant	23,009	767,681 (757,839-777,535)	0.42 (0.655)
In Situ	313	10,444 (9,204-11,597)	0.01 (5.652)
Benign	11,814	393,985 (386,927-401,100)	0.21 (0.918)
Unknown	847	28,242 (26,323-30,188)	0.02 (3.436)
Breast			
Malignant	18,447	614,898 (605,977-623,648)	0.33 (0.733)
In Situ	2,645	88,162 (84,859-91,486)	0.05 (1.943)
Benign	1,059	35,298 (33,134-37,367)	0.02 (3.071)
Unknown	40,430	1,347,538 (1,334,547-1,360,502)	0.73 (0.493)
Thyroid			
Malignant	38,038	1,268,011 (1,255,395-1,280,613)	0.69 (0.510)
In Situ	83	2,767 (2,209-3,313)	0.00 (10.975)
Benign	35,266	1,175,594 (1,163,357-1,187,839)	0.64 (0.529)
Unknown	2,747	91,559 (88,172-94,983)	0.05 (1.907)
Colorectal			
Malignant	20,011	667,706 (658,438-676,846)	0.36 (0.703)
In Situ	1,543	51,462 (48,964-54,118)	0.03 (2.546)
Benign	47,200	1,573,549 (1,559,488-1,587,651)	0.85 (0.457)
Unknown	940	31,344 (29,268-33,318)	0.02 (3.261)

***Mean age (SD) = 46.6 (17.73) years**

3.2 Top 5 Neoplasm Diagnoses of all adult patients

The total patient number with at least one neoplasm diagnosis of the top 5 cancers was 8,736,862 (4.7% of the total study population). Of those, the prevalence of the benign neoplasm of colon and rectum diagnosis (0.85%; RSE, 0.457) was the highest followed by neoplasm of uncertain or unknown behavior of breast (0.73%; RSE, 0.493), malignant neoplasm of thyroid gland (0.69%; RSE, 0.510), benign neoplasm of thyroid gland (0.64%; RSE, 0.529), and malignant neoplasm of stomach (0.42%; RSE, 0.655).

3.3 Prevalence of the nitrates use

Patients with at least one prescription claim for systemic nitrate product were 0.79% (n=1,445,227, RSE, 0.476) of the total studied population. More than half of the nitrate prescriptions were NTG (0.63%; RSE, 0.532).

3.3.1 Demographic Characteristics of the Nitrates Users

Of all nitrates users, the number of male patients with the nitrate prescription was higher than the female patients (n= 820,949 vs. 624,279). The mean age of the 1,445,227 patients was 63.7 years (SD, 14.85). The prevalence of the patients aged 65−79 years group comprised the largest portion and the most nitrates users were NHI insured. There were 534 patients (95% CI, 184−736) with obesity diagnosis and 568 patients (95% CI, 368−920) with smoking diagnosis. The number of patients with angina diagnosis was 821,773 which constituted 0.45% (RSE, 1.556) of the total population, and 57.0% of all

nitrates users (Table 5).

3.3.2 Top 5 Cancer Diagnoses of the Nitrates Users

Of all nitrates users, 149,705 (10.4% of all nitrates users) patients had at least one neoplasm diagnosis of the top 5 cancers. Of those, benign neoplasm of colon and rectum was the most common diagnoses followed by malignant neoplasm of colon and rectum, malignant neoplasm of stomach, malignant neoplasm of lung, and malignant neoplasm of stomach (Table 5).

Table 5. Demographic characteristics of the Nitrates users and non-users

	No			Nitrates[a,b]			NTG			ISMN			ISDN	
	Unweighted Number of pts (Unwgt)	Weighted Number of patients (Wgt) (95% CI)	Wgt % (RSE %)	Unwgt	Wgt (95% CI)	Wgt % (RSE %)	Unwgt	Wgt (95% CI)	Wgt % (RSE %)	Unwgt	Wgt (95% CI)	Wgt % (RSE %)	Unwgt	Wgt (95% CI)	Wgt % (RSE %)
Overall population visits	5,478,425	182,630,261 (182,616,691-182,643,750)	99.21 (0.004)	43,310	1,445,227 (1,431,739-1,458,798)	0.79 (0.476)	34,911	1,164,796 (1,152,681-1,176,979)	0.63 (0.532)	4,472	149,310 (144,867-153,703)	0.08 (1.494)	15,202	507,411 (499,397-515,411)	0.28 (0.808)
Gender															
Female	2,882,949	96,106,356 (96,097,529-96,115,201)	52.21 (0.005)	18,705	624,279 (615,364- 633,220)	0.34 (0.725)	14,932	498,270 (490,377- 506,208)	0.27 (0.813)	1,866	62,324 (59,456-65,163)	0.03 (2.312)	6,113	204,083 (198,986-209,110)	0.11 (1.275)
Male	2,595,476	86,523,906 (86,513,823-86,534,071)	47.00 (0.006)	24,605	820,949 (810,853-831,101)	0.45 (0.631)	19,979	666,525 (657,334-675,741)	0.36 (0.702)	2,606	86,985 (83,570-90,381)	0.05 (1.957)	9,089	303,328 (297,098-309,615)	0.16 (1.044)
Age group															
19-34	1,505,182	50,135,755 (50,120,810-50,150,631)	27.24 (0.015)	1,101	36,689 (34,606-38,840)	0.02 (3.012)	985	32,824 (30,741-34,790)	0.02 (3.184)	20	667 (368-920)	0.00 (22.360)	200	6,664 (5,706-7,547)	0.00 (7.070)
35-49	1,712,955	57,091,258 (57,068,372-57,114,022)	31.02 (0.020)	5,207	173,392 (168,613-178,001)	0.09 (1.383)	4,567	152,081 (147,629-156,464)	0.08 (1.478)	310	10,321 (9,204-11,413)	0.01 (5.679)	1,422	47,348 (44,914-49,884)	0.03 (2.651)
50-64	1,398,043	46,615,286 (46,592,636-46,637,918)	25.32 (0.025)	14,967	499,092 (491,113-507,128)	0.27 (0.813)	12,545	418,325 (411,041-425,583)	0.23 (0.889)	1,270	42,353 (39,944-44,730)	0.02 (2.805)	5,043	168,165 (163,459-172,847)	0.09 (1.405)
65-79	700,217	23,360,486 (23,336,906-23,384,030)	12.69 (0.051)	17,247	575,650 (567,137-584,072)	0.31 (0.754)	13,496	450,431 (442,886- 457,980)	0.24 (0.854)	2,099	70,063 (67,003-73,078)	0.04 (2.179)	6,578	219,595 (214,264-224,940)	0.12 (1.228)
80 and older	162,028	5,427,477 (5,409,242-5,445,689)	2.95 (0.171)	4,788	160,405 (155,912-164,932)	0.09 (1.434)	3,318	111,135 (107,316-114,863)	0.06 (1.727)	773	25,906 (24,114-27,795)	0.01 (3.592)	1,959	65,639 (62,770-68,476)	0.04 (2.252)
Public Insurance Scheme															
NHI	5,296,663	176,566,170 (176,536,125-176,596,134)	95.92 (0.009)	38,708	1,291,596 (1,278,772-1,304,359)	0.70 (0.504)	31,473	1,050,046 (1,038,554-1,061,563)	0.57 (0.560)	3,777	126,090 (122,042-130,141)	0.07 (1.625)	13,427	448,139 (440,493-455,771)	0.24 (0.860)
Medicaid	176,883	5,901,300 (5,874,585-5,928,151)	3.21 (0.232)	3,874	129,343 (125,355-133,455)	0.07 (1.605)	2,884	96,267 (92,774-99,769)	0.05 (1.860)	613	20,485 (18,776-22,089)	0.01 (4.038)	1,425	47,593 (45,098-50,069)	0.03 (2.647)
Veteran healthcare	4,879	162,791 (158,305-167,325)	0.09 (1.426)	728	24,288 (22,457-26,139)	0.01 (3.703)	554	18,483 (16,935-20,064)	0.01 (4.246)	82	2,735 (2,209-3,313)	0.00 (11.041)	350	11,679 (10,492-12,885)	0.01 (5.343)
Obesity	4,112	137,027 (2,299,940-2,334,064)	1.32 (0.376)	16	534 (184-736)	0.00 (25.000)	15	501 (184-736)	0.00 (25.820)	0	0 (0)	0.00 (-)	6	201 (0-368)	0.00 (40.825)
Smoking	509	16,966 (15,462-18,408)	0.01 (4.432)	17	568 (368-920)	0.00 (24.254)	17	568 (368-920)	0.00 (24.254)	2	67 (0-184)	0.00 (70.711)	6	200 (0-368)	0.00 (40.825)
Angina	108,668	3,625,787 (3,604,750-3,646,904)	1.97 (0.296)	24,629	821,773 (811,589-832,021)	0.45 (0.634)	20,251	675,621 (666,353-684,945)	0.37 (0.700)	2,937	98,034 (94,431-101,610)	0.05 (1.843)	9,836	328,250 (321,764-334,649)	0.18 (1.006)

(Table 5 Continued)

Lung															
Malignant	10,042	335,191 (328,575-341,644)	0.18 (0.995)	552	18,432 (16,935-19,880)	0.01 (4.255)	403	13,452 (12,149-14,726)	0.01 (4.980)	61	2,039 (1,473-2,577)	0.00 (12.806)	192	6,411 (5,522-7,363)	0.00 (7.216)
In Situ	90	3,009 (2,393-3,682)	0.00 (10.541)	3	101 (0-184)	0.00 (57.736)	1	34 (0- 184)	0.00 (100)	2	67 (0-184)	0.00 (70.712)	0	0 (0)	0.00 (-)
Benign	4,965	165,596 (161,066-170,270)	0.09 (1.418)	178	5,940 (5,154-6,811)	0.00 (7.496)	142	4,738 (4,050-5,522)	0.00 (8.391)	19	635 (368-920)	0.00 (22.942)	57	1,902 (1,473- 2,393)	0.00 (13.246)
Unknown	1,765	58,883 (56,143-61,665)	0.03 (2.379)	44	1,469 (1,104-1,841)	0.00 (15.077)	36	1,201 (736-1,657)	0.00 (16.669)	3	101 (0-184)	0.00 (57.736)	16	534 (184-736)	0.00 (25.000)
Stomach															
Malignant	22,397	747,240 (737,590-756,918)	0.41 (0.665)	612	20,441 (18,776- 22,089)	0.01 (4.041)	475	15,863 (14,358-17,303)	0.01 (4.587)	50	1,670 (1,289-2,209)	0.00 (14.145)	245	8,187 (7,179-9,204)	0.00 (6.388)
In Situ	298	9,943 (8,836-11,045)	0.01 (5.792)	15	501 (184 -736)	0.00 (25.820)	14	467 (184- 736)	0.00 (26.726)	0	0 (0)	0.00 (-)	5	168 (0-368)	0.00 (44.723)
Benign	11,526	384,375 (377,355-391,344)	0.21 (0.930)	288	9,610 (8,467-10,676)	0.01 (5.892)	235	7,841 (6,811- 8,836)	0.00 (6.523)	30	1,001 (552-1,289)	0.00 (18.256)	102	3,403 (2,761-4,050)	0.00 (9.902)
Unknown	824	27,474 (25,586-29,268)	0.01 (3.483)	23	768 (368-1,104)	0.00 (20.852)	18	600 (368-920)	0.00 (23.570)	1	33 (0-184)	0.00 (100)	8	268 (0-368)	0.00 (35.356)
Breast															
Malignant	18,286	609,527 (600,822-618,310)	0.33 (0.736)	161	5,371 (4,602-6,259)	0.00 (7.881)	126	4,202 (3,497-4,970)	0.00 (8.909)	12	400 (184-552)	0.00 (28.868)	54	1,803 (1,289-2,209)	0.00 (13.607)
In Situ	2,630	87,662 (84,307-90,933)	0.05 (1.948)	15	501 (184-736)	0.00 (25.820)	12	401 (184-552)	0.00 (28.867)	0	0 (0)	0.00 (0)	3	100 (0-184)	0.00 (57.735)
Benign	1,052	35,065 (32,950-37,183)	0.02 (3.083)	7	233 (0-368)	0.00 (37.797)	6	200 (0- 368)	0.00 (40.826)	1	34 (0-184)	0.00 (100)	3	100 (0-184)	0.00 (57.735)
Unknown	40,216	1,340,403 (1,327,368-1,353,323)	0.73 (0.494)	214	7,135 (6,259-8,099)	0.00 (6.836)	186	6,202 (5,338-7,179)	0.00 (7.332)	10	334 (184-552)	0.00 (31.623)	59	1,967 (1,473-2,393)	0.00 (13.017)
Thyroid															
Malignant	37,620	1,254,074 (1,241,405-1,266,623)	0.68 (0.512)	418	13,938 (12,517-15,278)	0.01 (4.891)	340	11,337 (10,124-12,517)	0.01 (5.423)	26	867 (552-1,289)	0.00 (19.612)	124	4,136 (3,497-4,786)	0.00 (8.980)
In Situ	80	2,667 (2,025-3,313)	0.00 (11.180)	3	100 (0-184)	0.00 (57.735)	2	66 (0-184)	0.00 (70.711)	1	33 (0-184)	0.00 (100)	0	0 (-)	0.00 (-)
Benign	34,925	1,164,222 (1,152,128-1,176,426)	0.63 (0.532)	341	11,372 (10,124-12,517)	0.01 (5.415)	297	9,904 (8,836-11,045)	0.01 (5.803)	15	500 (184-736)	0.00 (25.820)	82	2,735 (2,209-3,313)	0.00 (11.042)
Unknown	2,723	90,759 (87,436-94,247)	0.05 (1.916)	24	800 (552 -1,104)	0.00 (20.412)	21	700 (368-920)	0.00 (21.822)	2	67 (0-184)	0.00 (70.711)	9	300 (184-552)	0.00 (33.334)
Colorectal															
Malignant	19,368	646,232 (637,085-655,309)	0.35 (0.715)	643	21,474 (19,880-23,194)	0.01 (3.943)	497	16,600 (15,094-18,039)	0.01 (4.485)	73	2,439 (1,841-2,945)	0.00 (11.704)	227	7,579 (6,627- 8,652)	0.00 (6.637)
In Situ	1,509	50,327 (47,860-52,830)	0.03 (2.573)	34	1,134 (736-1,473)	0.00 (17.156)	23	768 (368-1,104)	0.00 (20.852)	3	100 (0-184)	0.00 (57.735)	11	367 (184-552)	0.00 (30.151)
Benign	46,315	1,544,031 (1,530,035-1,558,015)	0.84 (0.461)	885	29,518 (27,611-31,477)	0.02 (3.361)	728	24,280 (22,457-25,955)	0.01 (3.706)	76	2,536 (2,025-3,129)	0.00 (11.472)	278	9,274 (8,099-10,308)	0.01 (5.997)
Unknown	914	30,476 (28,532-32,397)	0.02 (3.308)	26	867 (552-1,289)	0.00 (19.612)	16	534 (184-736)	0.00 (25.000)	4	134 (0-184)	0.00 (50.000)	14	467 (184-736)	0.00 (26.726)

[a] Nitrates include NTG, ISMN, and ISDN

[b] Nitrates User Mean age (SD) = 63.70 (14.851) years

3.4 Associations between nitrates use and cancer diagnoses

The adjusted and unadjusted ORs were listed in Table 6. Overall, nitrates users were more likely to be recorded with neoplasm diagnoses. Especially, nitrates users were about 3 times more likely to have malignant neoplasm of lung diagnosis than non-users (Adjusted OR, 3.019; 95% CI, 2.724-3.346). The carcinoma *in situ* of stomach diagnosis was about 2.6 times higher in the nitrates users (Adjusted OR, 2.626; 95% CI, 1.405-4.910). Other neoplasms such as benign neoplasm of lung, neoplasm of uncertain or unknown behavior of colon and rectum, and malignant neoplasm of colon and rectum were about 2 times more likely to be diagnosed in the nitrates users (Table 6). Interestingly, ISMN and ISDN users were about 50% (Adjusted OR, 0.532; 95% CI, 0.319-0.886) and 20% (Adjusted OR, 0.792; 95% CI, 0.634-0.990), respectively, reduced likelihood to be diagnosed with benign neoplasm of thyroid gland (Table 7).

Table 6. Unadjusted and adjusted odds ratio (OR) of the all nitrates and top 5 neoplasms from weighted analysis

	Nitrates	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lung		
Malignant	7.028 (6.448-7.661)	3.019 (2.724-3.346)
In Situ	.. *	.. *
Benign	4.553 (3.920-5.289)	2.046 (1.718-2.435)
Unknown	3.156 (2.340-4.257)	1.273 (0.908-1.786)
Stomach		
Malignant	3.492 (3.221-3.786)	1.565 (1.432-1.712)
In Situ	6.373 (3.794-10.705)	2.626 (1.405- 4.910)
Benign	3.175 (2.824-3.570)	1.400 (1.234-1.589)
Unknown	3.533 (2.334-5.348)	1.552 (0.979-2.460)
Breast		
Malignant	1.114 (0.954-1.301)	1.201 (1.018-1.417)
In Situ	0.723 (0.435-1.200)	0.814 (0.473-1.402)
Benign	.. *	.. *
Unknown	0.673 (0.588-0.769)	1.210 (1.047-1.399)
Thyroid		
Malignant	1.411 (1.281-1.554)	1.364 (1.228-1.516)
In Situ	.. *	.. *
Benign	1.236 (1.111-1.376)	1.125 (1.001-1.266)
Unknown	1.114 (0.745-1.665)	1.052 (0.691-1.603)
Colorectal		
Malignant	4.249 (3.925-4.598)	1.857 (1.697-2.031)
In Situ	2.851 (2.029-4.005)	1.183 (0.815-1.718)
Benign	2.445 (2.286-2.615)	1.226 (1.140-1.320)
Unknown	3.598 (2.436-5.313)	1.940 (1.267-2.970)

* RSE (Relative Standard Error)≥ 30%, considered as statistically unreliable

Table 7. Unadjusted and adjusted odds ratio of the each nitrates and neoplasm of thyroid gland (Weighted Analysis)

	NTG		ISMN		ISDN	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Thyroid Cancer						
Malignant	1.424 (1.279-1.585)	1.340 (1.193-1.504)	0.842 (0.572-1.238)	0.892 (0.605-1.316)	1.186 (0.993-1.415)	1.187 (0.989-1.424)
In Situ	.. *	.. *	.. *	.. *	.. *	.. *
Benign	1.338 (1.194-1.501)	1.195 (1.055-1.353)	0.523 (0.315-0.868)	0.532 (0.319- 0.886)	0.843 (0.678-1.047)	0.792 (0.634- 0.990)
Unknown	1.210 (0.787-1.858)	1.127 (0.718-1.769)	.. *	.. *	1.191 (0.619-2.291)	1.196(0.620-2.306)

* RSE (Relative Standard Error)≥ 30%, considered as statistically unreliable

4. DISCUSSION

Due to the uncertain role of the nitrates in the cancer patients, a cross-sectional study evaluating the association between nitrates prescriptions and diagnoses with the top five cancers in Korea was conducted. In this study of 184,075,489 patients aged 19 years and older, 1,445,227 patients (0.79%) were identified as nitrates users. Of those, male patients were more likely to have nitrate prescriptions than female patients, and the highest proportion of the total nitrate prescriptions was accounted by the patients aged 65-79 years group. The most significant finding of our study is that the nitrates users were more likely to be recorded with neoplasm diagnoses, except benign neoplasm of thyroid gland, than non-users after the adjustment by age, gender, insurance, obesity, smoking and angina.

Although biologic plausibility is unclear, findings from our study indicate a positive correlation between nitrates use and the neoplasm diagnoses. This is quite consistent with *in vitro* studies demonstrating pro-tumorigenic effects of NO. The effect of NO on cellular proliferation or tumor growth was shown in the human NSCLC cells and breast cancer cells study.

In a study of NO and human NSCLC cells performed by Yongsanguanchai et al. reported that the exposure of NO gradually altered the cell morphology and promoted cancer stem cell-like phenotypes in human lung cancer cells. The effect was

caused by caveolin-1 upregulation which is responsible for the aggressive behavior of the cells [25]. Moreover, in the NO and human breast cancer cell study, Pervin et al. reported that a exposure of human breast cancer cell lines to NO (DETA-NONOate at 30-60 μmol/L) increased total protein synthesis and proliferation [26].

Other pro-tumorigenic effects such as angiogenesis and metastasis were also shown in the *in vitro* studies. In the prostate cancer cell study conducted by Polytarchou et al., exogenously added or endogenously produced NO led the expression of pleiotrophin, a growth factor involved in angiogenesis and tumor growth, and cell migration [27].

However, there are several *in vitro* studies that proposed anti-tumorigenic effects of NO such as apoptosis and tumor growth inhibition. Due to these inconsistent results, more explicit studies to examine NO effect on cancer by varying nitrates dosage or host factors are needed.

Another finding of our study was that ISMN and ISDN users were less likely to be diagnosed with benign neoplasm of thyroid gland. Based on current literature, clear explanations on delineating the association between the tumor and nitrate products are lacking except a study reporting a negative correlation between nitrates and the benign neoplasm of thyroid gland was shown whereas malignant neoplasm showed positive correlation. Sousa et al. suggested that, by working together,

arginase 2(ARG2) and endothelial NOS(eNOS) that synthesize NO, could promote thyroid cancer cell proliferation, cell viability, and angiogenesis. In benign tumors, ARG2 was found to be down-regulated while overexpression was found in nearly all follicular thyroid carcinoma. Since eNOS was consistently expressed, the absence of ARG2-overexpression in benign tumors might be responsible for contrasting results. However, further study is needed for the definite mechanism of action of NO in thyroid tumor [28].

The major strength of the present study is a large sample size reflecting the entire national population. In addition, our study has a novelty due to a scarcity of information regarding nitrates and cancer research using big-data. Recently, this type of translational research which applies findings generated from pre-clinical studies to human studies [29] has been actively investigated. One representative example is the studies of statins, HMG-CoA reductase inhibitors used for the control of hypercholesterolemia [30], and cancers. In pre-clinical studies, statins were shown to have anticancer properties [30-32]. So, several observational studies such as cohort studies using big-data have been conducted to explore the association between statins and cancers [33-37]. Unlike a number of studies on statins, we believe that our study as an explorative study evaluating the effects of nitrates on cancer developments is innovative due to its originality and scarcity, especially using population level big-data.

Moreover, although a plausible pharmacological mechanism is unknown, there was a new finding that ISMN and ISDN users were less likely to be diagnosed with benign neoplasm of thyroid gland. Benign neoplasms are not cancerous, so they often not considered as seriously. However, enlarged benign tumor can be by pressing on vital organs [38]. As the fourth most common diagnosis in our study population, the association between benign neoplasm of thyroid gland and ISMN or ISDN is worthwhile to be investigated.

Several limitations should be considered in interpreting our study results. The main limitation is a low validity. Since this was a cross-sectional study, the study results were limited by the uncertainty in causal inference. This problem is primarily caused by the limitation of the study data, HIRA-NPS. Although HIRA database is highly efficient and can provide nationwide statistics, patient's de-identified number in HIRA database is different every year. Thus, longitudinal study is difficult to perform with HIRA-NPS.

Another limitation is the potential underestimation in the number of obese patients and smokers. Since obesity and smoking are the critical risk factors for most cancers, the patients' number from the database should be close to the actual number. In HIRA-NPS, patients' obesity and smoking status can be verified only if they were recoded with diagnostic codes for the treatments. However, there is a possibility of absence of the records as some patients with obesity and

smokers may have not received the treatments or truncation bias as only up to two diagnostic codes (major and secondary diagnosis) were available per claim. Therefore, possibility of misclassification should be considered when findings from the study are interpreted.

5. CONCLUSION

In conclusion, the results of our study showed that the nitrate users were more likely to have cancer diagnoses, except benign neoplasm of thyroid gland. Although controversies still persist regarding the effect of NO, there are substantial evidences that support a positive association between NO and its pro-tumorigenic effects. However, further research that examines the links between nitrates and the cancers is still needed for the development of effective disease prevention and treatment strategies. For example, cohort studies using patient medical records or big-data that are similar to the preceding studies regarding statins and cancers can be conducted. Moreover, exploration of the questionable effect of the ISMN or ISDN in the benign neoplasm of thyroid gland needs to be conducted.

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국 문 초 록

암은 전 세계적으로 높은 사망률과 유병률의 주원인으로 알려져 있으며, 암질환 관련 의료비 및 사회적 부담 또한 매우 크므로, 효과적인 암의 진단, 예방 및 치료방법 개발이 시급하다. 최근 신약개발 절차가 까다로워지면서 시판 중인 약물 또는 산업화에 실패한 약물을 대상으로 새로운 적응증을 규명하는 신약재창출(Drug Repositioning) 연구가 수행되고 있는데, 기초 및 임상 연구를 통하여 항암 효과를 보일 수 있다고 알려진 질산염제제(Nitrates)도 신약재창출을 통한 항암제 후보약물로써 제안되고 있다. 하지만, 항암치료에 있어 질산염제제의 효과에 대한 선행연구들이 상반된 결과를 제시함으로, 본 연구에서는 질산염제제의 효과를 규명하고자 질산염제제 사용자와 우리나라에서 발병률이 가장 높은 상위 5가지 암(악성 신생물) 및 관련 신생물 진단과의 연관성을 질산염제제 비사용자와 비교, 분석하는 역학연구를 수행하였다.

이 연구는 단면적 연구로서 2010년-2014년 건강보험심사평가원 전체환자 표본자료(HIRA-NPS)를 활용하여 만 19세 이상 성인 환자를 대상으로 하였으며, 연구기간 동안 질산염제제를 처방 받은 환자 그룹과 처방 받지 않은 환자 그룹의 우리나라 발병률 상위 5대 암 부위인 갑상선, 위, 대장, 폐, 또는 유방의 신생물 진단 현황을 비교하였다. 질산염제제로는 nitroglycerin(NTG), isosorbide mononitrate (ISMN), isosorbide dinitrate(ISDN)이 사용되었다. 모든 분석은 국가차원 환자 데이터로 반영하기 위하여 가중치를 사용하여 분석하였다.

전체환자 표본자료 분석결과, 2010년에서 2014년까지 만 19세 이상 성인 의료이용자는 184,075,489명이었다. 이 중 질산염제제를 처방 받은 환자는 총 1,445,227명(0.79%; RSE, 0.476)이었으며, 질

산염제제 사용자 중 상위 5대 신생물 (악성, 제자리, 양성, 행동양식 불명 또는 미상의 신생물) 진단을 받은 환자는 총 8,736,862명 이었다. 이 환자들을 대상으로 교란변수(성별, 나이, 의료보장 형태, 비만, 흡연, 협심증)를 보정하여 각각의 질산염제제 처방과 상위 5대 신생물 진단을 로지스틱 회기분석한 결과, 질산염제제 비사용자보다 질산염제제 사용자에게서 대부분의 상위 5대 신생물 진단이 많은 것으로 나타났다. 하지만, ISMN (Adjusted OR, 0.532; 95% CI, 0.319−0.886)와 ISDN (Adjusted OR, 0.792; 95% CI, 0.634−0.990) 사용자들에게서는 갑상선 양성 신생물 진단이 비사용자들에 비하여 적은 것으로 나타났다.

본 연구에서는 질산염제제 사용자들과 상위 5대 신생물 진단 사이에 높은 연관성이 나타났다. 하지만, 단면적 상관성을 평가하는 본 연구의 방법론적 한계점을 고려하여 신생물 치료에 있어 질산염제제의 정확한 효과를 규명하기 위해 향후 체계적인 기초 및 임상 연구의 수행이 필요하다.

주요어 : 질산염제제, 암, 단면적 연구, 신약재창출, HIRA
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