Menopausal hormone replacement therapy and gastrointestinal cancer risks based on a nationwide cohort data

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Directed by Professor Eun-Cheol Park

The Doctoral Dissertation
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Ji Hyung Nam

June 2019

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June 2019

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to Professor Eun-Cheol Park for his dedicated guidance and mentorship. He has been a great mentor. I was fortunate to learn from Professor Eun-Cheol Park of Yonsei University. The enthusiastic teaching of Professor Eun-Cheol Park and other professors in the Department of Preventive Medicine made me feel joy and accomplishment in my studies.

I would like to thank Professor Chung Mo Nam, Professor Jin Ho Lee, Professor Sohee Park, and Professor Sung-In Jang for their criticisms and thoughtful suggestions. Also, I would like to thank Professor Sung-In Jang and assistant teacher Jaeyong Shin for their detailed teaching in the overall research process.

I would like to express my sincere gratitude to Professor Jin Ho Lee and other professors in the Department of Gastroenterology at Dongguk University for their supports and encouragements for my studies and work. I am also grateful that Professor Hyun Soo Park in the Department of Obstetrics and Gynecology at Dongguk University offered invaluable assistance for academic understanding.

At last, I would like to express my special thanks to my family for their constant love and endless encouragements.

June, 2019

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ABSTRACT

Menopausal hormone replacement therapy and gastrointestinal cancer risks based on a nationwide cohort data

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Background: Exogenous female hormones play a protective role against intestinal carcinogenesis. However, clinical studies to support the mechanisms show conflicting results, and most studies have been conducted in the West. This study investigates the association between hormone replacement therapy (HRT) and gastrointestinal (GI) cancer in South Korea, and assesses the dose-response relationship.

Methods: A prescription-based matched cohort study was conducted using the National Health Insurance Service Sample Cohort (2002-2013) of South Korea. We used 1:5 propensity score matching, and 133,690 women (22,577 HRT users and 111,113 non-users) were selected. The main comparison was the rate of GI cancer incidence between HRT users and non-users. Kaplan-Meier survival curves with log-rank tests were used. Cox proportional hazard models were used to estimate hazard ratios (HR) with 95% confidence intervals. The final model included age, region, income, Charlson comorbidity index, and the year of study entry. Subgroup analyses were performed based on HRT regimens and doses. Landmark analysis was used to determine dose-response relationship.

Results: The median follow-up was 79.6 of months. Kaplan-Meier survival curve showed less frequent GI cancer diagnoses in HRT users

compared to non-users (0.13 vs. 0.16 per 100,000 person-years, log-rank *p*=0.0089). Multivariate analysis showed HRT was significantly associated with decreased incidence of GI cancer (HR, 0.809; *p*=0.0081) and colorectal cancer (HR, 0.757; *p*=0.0457). The association of HRT with gastric cancer incidence was marginally significant (HR, 0.787; *p*=0.0733). The mortality from GI cancer was also lower in HRT users than in non-users (HR, 0.737; *p*=0.0445). The relationship between HRT and GI cancer was more clear in higher HRT dose in terms of both incidence (*p* for trend=0.0002) and mortality (*p* for trend=0.0064).

Conclusions: Postmenopausal HRT was associated with decreased risk of GI cancer. This negative association showed dose-response relationship.

Keywords: hormone replacement therapy, gastrointestinal cancer, colorectal cancer, survival analysis

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I. INTRODUCTION

Gastrointestinal (GI) cancer refers to malignancy originating from the GI tract, biliary system, or pancreas. Even though the incidence of GI cancer has been on the decline or plateaued with national interest in cancer screening and surveillance, GI cancers are still a major cause of cancer incidence and mortality worldwide [1]. As the incidence of GI cancer typically increases with age, it may become a major health issue in today's aging society. Most GI cancers are more prevalent in men than women [1]. However, its prevalence rapidly increases with age, even in women. This suggests that female sex hormones protect against GI cancer. According to recent cancer statistics, in South Korea, among women aged 65 years or older, the first and second most common cancers are colorectal and stomach cancer, respectively [2]. These statistics demonstrated GI cancer incidence in postmenopausal Korean women rising rapidly.

In the West, hormone replacement therapy (HRT) is widely used as a treatment for postmenopausal symptoms and menopause-related disorders such as osteoporosis. However, globally their use has declined over the past decades, following reports of associated increased risk of breast cancer [3]. The estimated rate of HRT use in women aged 45-69 years old was 2-9% in European countries in 2010 [4]. In the same year, the annual statistics of Health Insurance in Korea reported that approximately 4.5% of women older than 50

years used HRT [5], comparable to the rate of Western countries [4].

Several studies reported that exogenous female hormones play a role in intestinal carcinogenesis [6,7]. Thus, female HRT may reduce the incidence of GI cancers, of which the increase in incidence with age precipitates after menopause. Since randomized controlled trials (RCT) showed that HRT reduces the risk of colorectal cancer (CRC) [8,9], additional RCTs and many observational studies supported the protective effect of HRT on CRC [10-12]. However, the evidence from clinical studies is inconclusive because other studies reported no reduction of the risk of CRC associated with HRT [13-15]. The number of studies on gastric cancer (GC) risk associated with HRT is lower than CRC probably because of the low incidence of GC in the West. Recent studies reported that HRT also reduces the risk of GC [16,17]. However, there are few studies covering the entire spectrum of GI cancers [18]. Moreover, almost all the research so far has been conducted in the West. No large-scale population-based studies have been conducted in the East, where the characteristics of the population, the risk factors, and the cancer prevalence may be different from the West. The prevalence of GC is high in South Korea, and CRC is currently increasing [1,19]. Thus, the aim of this study was to conduct a large-scale cohort study representing the general population of Korea, using National Health Insurance Service (NHIS) Sample Cohort database. The study hypothesis is that HRT use and the incidence of GI cancers are associated, and that there is a dose-response relationship between the two.

II. MATERIALS AND METHODS

1. Study population

The data used in the study were from the NHIS Sample Cohort (2002-2013) of South Korea, a sample of approximately 1,000,000 individuals representative of the general population. The database provides individual patient information such as age, sex, disability or death-related data, residence, income level, insurance coverage, and all medical claim data since 2002. Among the 512,082 women who were registered in the National Sample Cohort in 2002, we first excluded patients who were prescribed HRT or those who visited a hospital with any cancers between 2002 and 2003 in order to washout previous HRT use or history of cancer diagnosis before 2004 (Figure 1). A diagnosis of any cancer was determined by the International Classification of Diseases 10th (ICD-10) C

code. Using the baseline cohort (n=485,612) after a two-year (2002, 2003) washout, we selected cases who received HRT between January 2004 and December 2013 (n=36,025). We included only HRT regimens with oral administration. The date of cohort entry in the cases was determined as the first date of HRT prescription. We additionally excluded cases diagnosed with any cancers or who died before the date of cohort entry, and those younger than 40 years old. Using 27,974 HRT users, we matched 1:5 control persons using propensity score matching, adjusting for age (5-year intervals), region (metropolitan or other region), and income level (four categories). The income level was determined based on the insurance coverage claim data. The entire South Korea population is mandated to enroll in National Health Insurance and pay insurance premium based on their salary or property. The income level was classified as less than 30% (low income), 31-60%, 61-90%, and more than 91% (high income).

After exclusions, 22,577 HRT users and 112,885 non-users were matched. The date of cohort entry in the non-users was set to the same date of first HRT prescription for each matching case. In the matched controls, the patients who were diagnosed with any cancers or died before the date of cohort entry were excluded, as with the HRT users. Finally, we selected 111,113 non-users who did not use HRT during the study period. ‘Event’ was defined as the development of any type of cancer after study entry. ‘Censored' included individuals who died before the end of the study. The study period was from the date of cohort entry to ‘Event’ or ‘Censored’, or otherwise when the end of the study was reached (December 31, 2013) for both HRT users and matched non-users. This study was approved by the Institutional Review Board, Dongguk University Ilsan Hospital (2018-09-010).

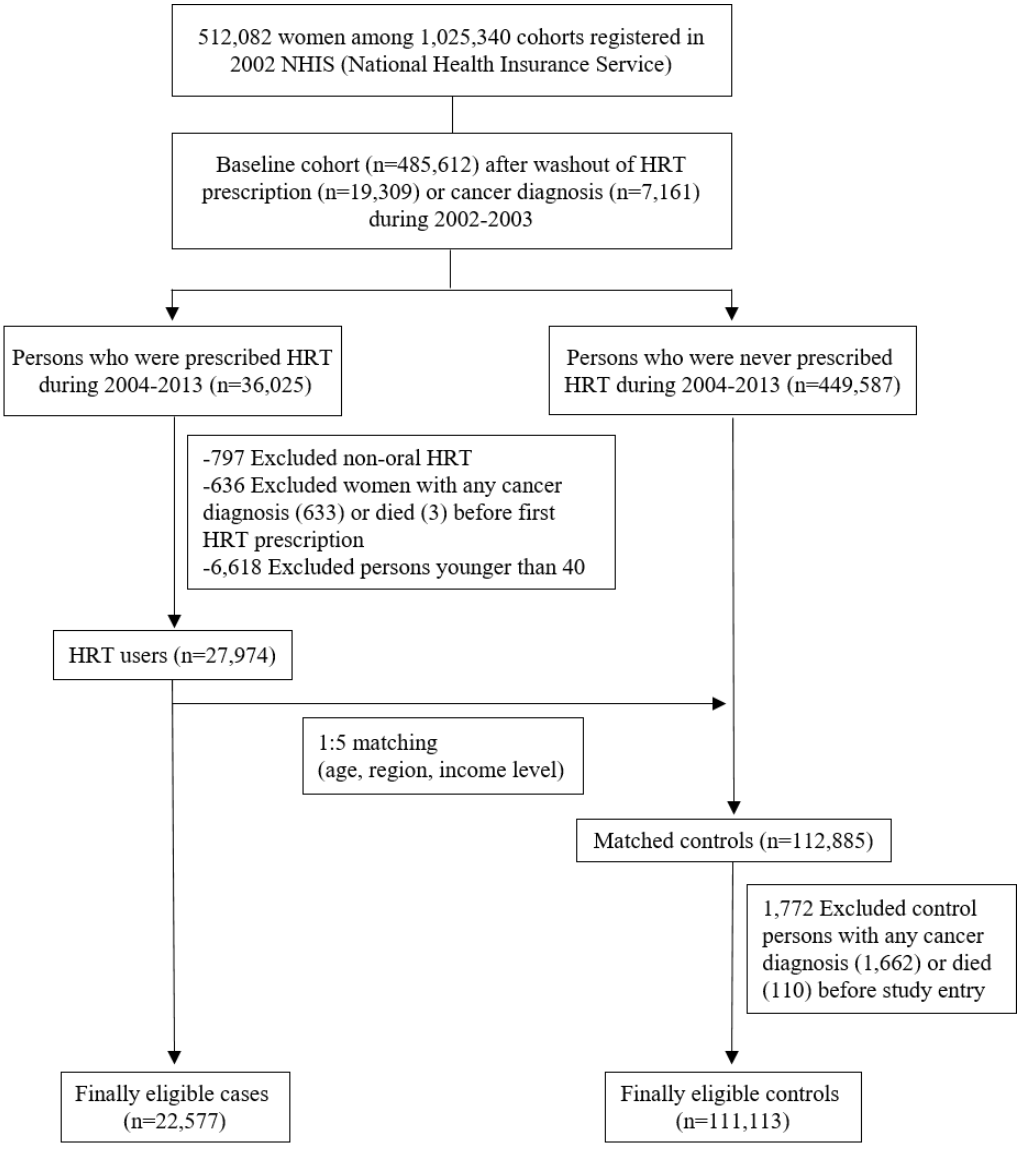

Figure 1. Study flow

2. Variables

The main outcome variable was diagnosis of GI cancer. A diagnosis of cancer

was determined by ICD-10 code in the medical statement of claim data. Gastrointestinal cancers included esophageal (ICD-10 C15), stomach (ICD-10 C16), small intestinal (ICD-10 C17), colorectal (ICD-10 C18 to C20), liver, gall bladder, biliary duct (ICD-10 C22 to C24), and pancreatic (ICD-10 C25) cancer. Secondary outcomes were a diagnosis of any type of cancer, all-cause mortality, and death from any type of cancer or GI cancer.

The use of HRT, the independent variable of interest, corresponded to Anatomical Therapeutic Chemical (ATC) codes; G03C, G03F, and G03H. The HRT prescription codes included estradiol (E2), conjugated equine estrogen (CEE), and tibolone. Tibolone, a selective estrogen receptor modifier (SERM), is commonly prescribed as HRT for menopausal women with a uterus. Hormone replacement therapy types were classified as estradiol, conjugated estrogen, tibolone, or mixed-type HRT. We also divided the HRT regimens into single (estradiol or CEE alone) or combination (estradiol plus progesterone or CEE plus progesterone, etc.) regimens. Total HRT doses in each case were calculated using the equivalent dose of estrogen. As the relative potency of estradiol 1.0 mg is equal to that of conjugated estrogen 0.625 mg, this equivalent dose was regarded as a defined daily dose (DDD). Because tibolone does not have a comparable standard for relative potency, a standard dose of 2.5 mg per tablet was considered as a DDD.

Other independent variables included Charlson comorbidity index (CCI), the year of study entry, age (10-year interval), income level, and region. The year of study entry refers to the year corresponding to the date of the cohort entry. The CCI was calculated by scoring the comorbid conditions that could affect patients' health outcomes, and categorizing into four groups from 1 (low risk) to 4 or more (high risk).

3. Statistical analyses

Independent sample *t*-tests or chi square tests were used to compare baseline characteristics between HRT users and non-users. Cancer incidence and mortality rates were shown at a rate per 100,000 person-years. The association of cancer incidence with HRT use and other covariates was investigated using chi square tests. We used log-rank test and Kaplan-Meier survival curve to compare cancer incidence between HRT users and non-users. We performed a survival analysis using Cox proportional hazard model with hazard ratio (HR) and 95% confidence interval (CI) to identify the association of HRT use with GI cancers, after adjusting for other independent variables. We performed subgroup analyses according to age, income level, region, and CCI score to identify how

the HRs from cox models are different by baseline characteristics. We also compared the all-cause mortality and cancer mortality between HRT users and non-users using the survival analyses. For the survival analyses, HRT use was categorized by types (E2, CEE, and tibolone), single or combination, and total dose. We used Landmark analysis[20] for the dose-response relationship of HRT with cancers. *P* values for trend was also identified. Landmark time point was set two years after the first HRT prescription date. Subjects who were diagnosed with any cancers or died within the time point were excluded. Total HRT dose was calculated within the time point, only. In addition, the Landmark data set was used for sensitivity analysis in terms of the relationship between HRT use and GI cancer. All statistical analyses were performed using SAS statistical software version 9.4 (Cary, NC).

III. RESULTS

1. Baseline characteristics

There were 133,690 (831,311 person-years) women in the study. The median follow-up time (Q1, Q3) was 79.6 months (45.8, 106.5); 79.3 months (45.5, 106.5) in HRT users and 79.6 (45.9, 106.6) in non-users. The mean follow-up time (standard deviation) was 74.6 months (36.8), which was not different between HRT users and non-users (p=0.2916, p for equality of variances: 0.4020). There was no significant difference between HRT users and non-users in terms of age, income level, region, and year of study entry (Table 1). Charlson comorbidity index was higher in non-users than HRT users (p<.0001).

2. Cancer incidence: bivariate analysis

Table 2 indicates the diagnosis of cancer based on HRT use and baseline characteristics. During the study period, 4,756 (0.57 per 100,000 person-years) subjects were diagnosed with any type of cancer. The rate of any cancer diagnosis was not different between HRT users and non-users (0.60 vs. 0.57, p=0.1699). Gastrointestinal cancers were diagnosed in 1,290 (0.155) subjects during the study period. The rate of GI cancer diagnosis was lower in HRT users than in non-users (0.13 vs. 0.16, p=0.0074). By each GI cancer type, CRC was less frequently diagnosed in HRT users than in non-users (0.04 vs. 0.06, p=0.0480), GC did not differ by HRT use (0.05 vs. 0.06, p=0.0828). The diagnosis of esophageal, hepatobiliary, and pancreatic cancer was not different between HRT users and non-users. In GI cancers except for esophageal cancer,

cancer incidence was significantly positively associated with age or CCI score. Gastrointestinal cancer and CRC were more frequently diagnosed in metropolitan areas than in other regions (p=0.0213, and p=0.0188, respectively), but was not associated with income level.

Table 1. Comparison between HRT users and non-users

Variables	Total (n=133,690)		HRT				*p* value
			Yes (n=22,577)		No (n=111,113)		
Follow-up months, mean (SD)	74.6 (36.8)		74.4 (36.9)		74.7 (36.7)		0.2916
Age (Years)	n	%	n	%	n	%	0.9745
40-49	65,008	48.63	10,959	48.54	54,049	48.64	
50-59	50,866	38.05	8,590	38.05	42,276	38.05	
60-69	12,902	9.65	2,189	9.70	10,713	9.64	
70~	4,914	3.68	839	3.72	4,075	3.67	
Income level							0.4772
≤30% (low)	38,082	28.49	6425	28.46	31,657	28.49	
31-60%	38,390	28.72	6575	29.12	31,815	28.63	
61-90%	33,180	24.82	5555	24.60	27,625	24.86	
≥91% (high)	24,038	17.98	4022	17.81	20,016	18.01	
Region							0.7807
Metropolitan	63,621	47.59	10,725	47.50	52,896	47.61	
Others	70,069	52.41	11,852	52.50	58,217	52.39	
CCI							<0.0001
1	45,068	33.71	8,040	35.61	37,028	33.32	
2	39,650	29.66	7,364	32.62	32,286	29.06	
3	15,894	11.89	2,994	13.26	12,900	11.61	
4 or more	33,078	24.74	4,179	18.51	28,899	26.01	
Year of study entry							0.9954
2004	19,707	14.74	3,293	14.59	16,414	14.77	
2005	18,744	14.02	3,142	13.92	15,602	14.04	
2006	16,350	12.23	2,750	12.18	13,600	12.24	
2007	17,018	12.73	2,871	12.72	14,147	12.73	
2008	14,815	11.08	2,507	11.10	12,308	11.08	
2009	10,375	7.76	1,754	7.77	8,621	7.76	
2010	11,128	8.32	1,891	8.38	9,237	8.31	
2011	8,076	6.04	1,374	6.09	6,702	6.03	
2012	9,489	7.10	1,623	7.19	7,866	7.08	
2013	7,988	5.98	1,372	6.08	7,866	5.95	

CCI, Charlson comorbidity index; HRT, hormone replacement therapy; SD, standard deviation.

Table 2. Incidence* of cancers according to HRT and baseline characteristics

	Total	Any cancer		GI			Esophageal		Gastric			Colorectal			Hepatobiliary			Pancreas		
	(person-years)	N	rate	N	rate		N	rate	N	rate		N	rate		N	rate		N	rate	
HRT																				
Yes	139,946	838	0.60	182	0.13	‡	0	0	65	0.05		60	0.04	†	40	0.03		16	0.01	
No	691,365	3,918	0.57	1,108	0.16		4	0.0006	403	0.06		388	0.06		237	0.03		68	0.01	
Age (Years)																				
40-49	378,667	1,883	0.50	§ 337	0.09	§	0	0	147	0.04	§	120	0.03	§	50	0.01	§	16	0.00	§
50-59	343,559	2,070	0.60	583	0.17		3	0.0009	206	0.06		200	0.06		137	0.04		32	0.01	
60-69	82,138	544	0.66	227	0.28		1	0.0012	77	0.09		77	0.09		52	0.06		19	0.02	
70~	26,946	259	0.96	143	0.53		0	0	38	0.14		51	0.19		38	0.14		17	0.06	
Income level																				
≤30%	238,266	1,527	0.64	§ 394	0.17		0	0	142	0.06		132	0.06		91	0.04		25	0.01	
31-60%	244,018	1,318	0.54	388	0.16		2	0.0008	144	0.06		139	0.06		82	0.03		19	0.01	
61-90%	206,359	1,154	0.56	295	0.14		2	0.0010	105	0.05		102	0.05		60	0.03		23	0.01	
≥91%	142,668	757	0.53	213	0.15		0	0	77	0.05		75	0.05		44	0.03		17	0.01	
Region																				
Metropolitan	397,177	2,398	0.60	§ 655	0.16	†	3	0.0008	233	0.06		238	0.06	†	131	0.03		46	0.01	
Others	434,134	2,358	0.54	635	0.15		1	0.0002	235	0.05		210	0.05		146	0.03		38	0.01	
CCI																				
1	259,391	1291	0.50	§ 232	0.09	§	0	0	103	0.04	§	82	0.03	§	33	0.01	§	10	0.00	§
2	260,853	1537	0.59	391	0.15		1	0.0004	153	0.06		135	0.05		79	0.03		21	0.01	
3	105,442	682	0.65	240	0.23		2	0.0019	79	0.07		86	0.08		55	0.05		17	0.02	
4 or more	205,624	1246	0.61	427	0.21		1	0.0005	133	0.06		145	0.07		110	0.05		36	0.02	
Total	831,311	4,756	0.57	1,290	0.16		4	0.0005	468	0.06		448	0.05		277	0.03		84	0.01	

CCI, Charlson comorbidity index; GI, gastrointestinal; HRT, hormone replacement therapy

* The incidence rates were calculated per 100,000 person-years

† $p<.05$, ‡ $p<.01$, § $p<0.001$

Figure 2 shows the Kaplan-Meier survival curves to compare the incidence of cancers between HRT users and non-users. Vertical lines indicate survival from diagnosis of cancer, and horizontal lines indicate observation years. Hormone replacement therapy users were significantly less frequently diagnosed with GI cancers (p=0.0089). Survival curves show marginal significance in the negative association of HRT use with GC (p=0.0887) and CRC (p=0.0517).

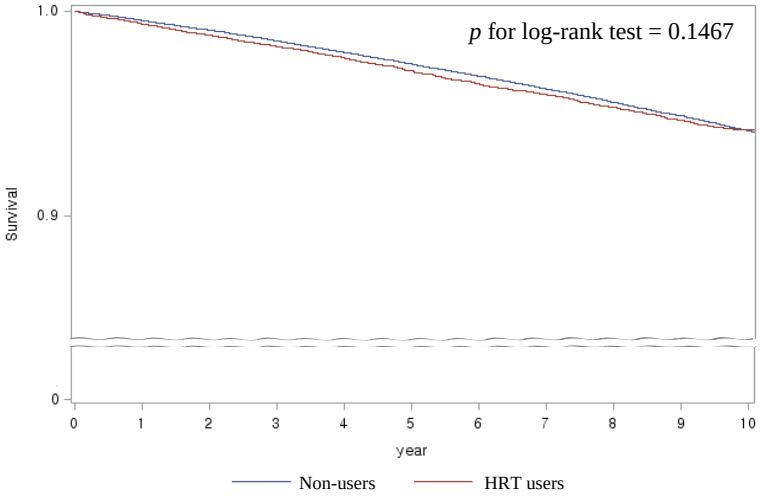

Figure 2-1. Kaplan-Meier survival curves for any cancer incidence

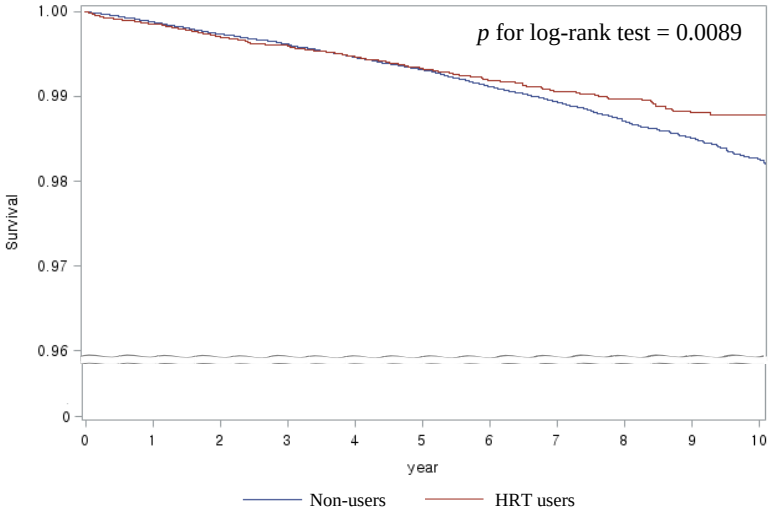

Figure 2-2. Kaplan-Meier survival curves for gastrointestinal cancer incidence

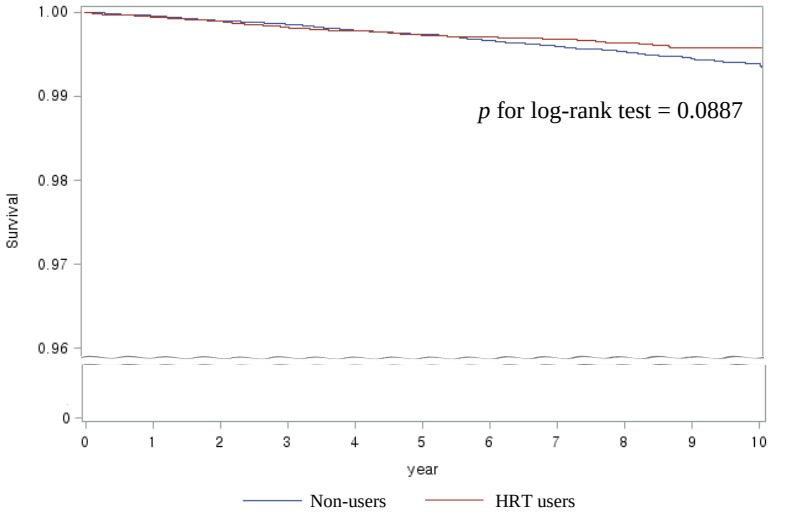

Figure 2-3. Kaplan-Meier survival curves for gastric cancer incidence

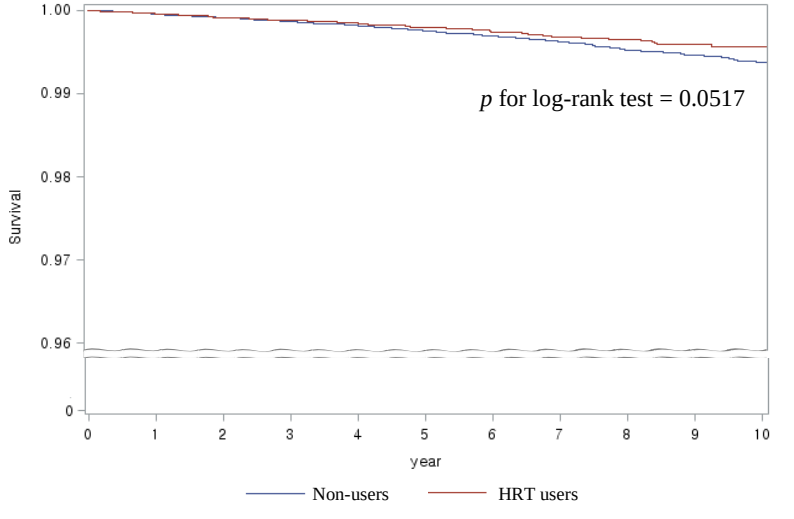

Figure 2-4. Kaplan-Meier survival curves for colorectal cancer incidence

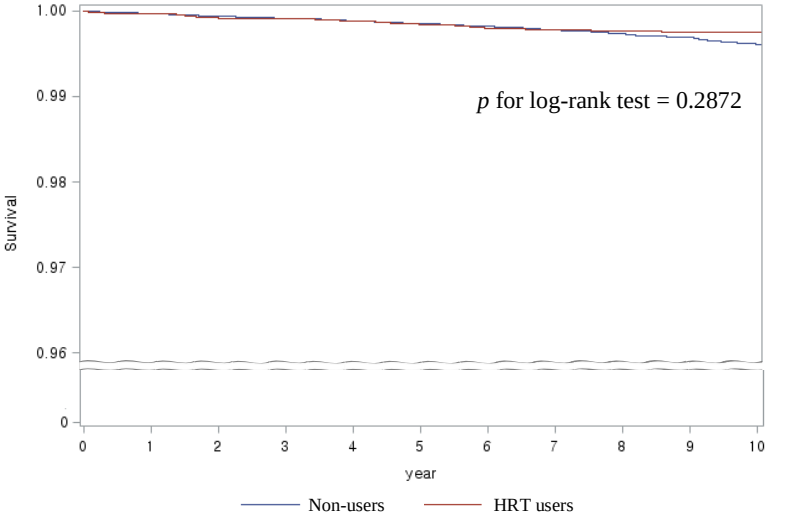

Figure 2-5. Kaplan-Meier survival curves for hepatobiliary cancer incidence

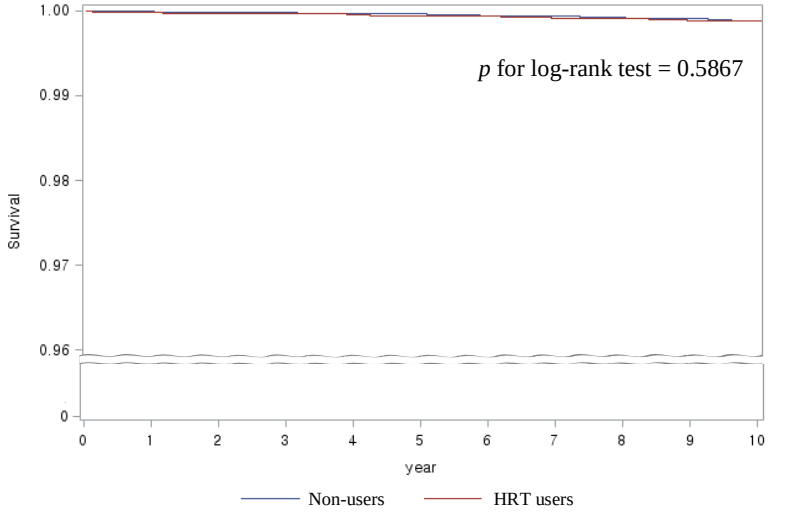

Figure 2-6. Kaplan-Meier survival curves for pancreatic cancer incidence

3. Cox proportional hazard model: multivariate analyses

Table 3 indicates the survival analyses using the Cox proportional hazard model to determine the relationship between HRT use and the incidence of cancer. The multivariate model included age group, income, region, CCI, and year of study entry. Survival analysis for esophageal cancer was not performed because there were too few cases. Hormone replacement therapy was negatively associated with the diagnosis of GI cancer (HR, 0.809; 95% CI, 0.691 to 0.946, p=0.0081). By cancer type, HRT use was significantly negatively associated with CRC diagnosis (HR, 0.757; 95% CI, 0.577 to 0.995, p=0.0457), the negative association between HRT use and GC diagnosis showed marginal significance (HR, 0.787; p=0.0733), but there was no significant association between HRT use and hepatobiliary or pancreatic cancer (HR, 0.847 and HR, 1.163, respectively). The diagnosis of any type of cancer or all GI cancers increased with age. Women in the upper income level showed lower rates of any cancer diagnosis than those with less than 30% of income. The rate of any cancer or CRC diagnosis was higher in metropolitan areas compared to other regions. The CCI score, which was significantly associated with cancer diagnosis in the bivariate analysis, was not associated after adjusting for other covariates.

4. Subgroup analyses by HRT regimens

Table 4 shows survival analyses by HRT regimen (type, combination) using the Cox proportional hazard model. There was no significant difference by HRT type. Meanwhile, HRT with only estrogen was significantly associated with increased incidence of any type of cancer (HR,1.258; p=0.0015). Furthermore, HRs in only estrogen regimen were more than 1.0 in most cancers however, HRs in combination regimen were less than 1.0. Especially, HR for pancreatic cancer diagnosis was significantly increased in HRT users with only estrogen compared to non-users (HR, 2.536; p=0.0196).

5. Subgroup analyses by baseline characteristics

Table 5 shows the subgroup analyses by the characteristics of the study population using the Cox proportional hazard model. There were no remarkable differences or tendencies that affected the relationship between HRT use and cancer incidence according to these characteristics.

Table 3-1. Hazard ratios for development of cancers: multivariate analyses

	Any cancer			GI			Gastric		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
HRT									
No	1.000			1.000			1.000		
Yes	1.053	0.977, 1.134	0.1800	0.809	0.691, 0.946	0.0081	0.787	0.605, 1.023	0.0733
Age (Years)									
40-49	1.000			1.000			1.000		
50-59	1.198	1.088, 1.318	0.0002	1.944	1.568, 2.411	<.0001	1.548	1.104, 2.172	0.0113
60-69	1.296	1.142, 1.472	<.0001	2.890	2.255, 3.702	<.0001	2.532	1.692, 3.790	<.0001
70~	1.959	1.685, 2.278	<.0001	6.052	4.662, 7.856	<.0001	4.119	2.621, 6.474	<.0001
Income level									
-30% (low)	1.000			1.000			1.000		
31-60%	0.855	0.794, 0.921	<.0001	1.008	0.876, 1.110	0.4551	1.026	0.813, 1.295	0.8307
61-90%	0.899	0.833, 0.971	0.0068	0.953	0.819, 1.110	0.5394	0.921	0.715, 1.188	0.5273
+91% (high)	0.841	0.770, 0.918	0.0001	0.938	0.793, 1.255	0.1839	0.939	0.710, 1.242	0.6592
Region									
Metropolitan	1.000			1.000			1.000		
Others	0.905	0.855, 0.959	0.0006	0.879	0.787, 0.981	0.0211	0.919	0.766, 1.103	0.3653
Charlson comorbidity index									
1	1.000			1.000			1.000		
2	1.021	0.914, 1.141	0.7124	0.926	0.718, 1.194	0.5509	1.008	0.682, 1.491	0.9674
3	1.069	0.938, 1.218	0.3155	1.094	0.830, 1.441	0.5242	0.961	0.618, 1.494	0.8587
4+	0.989	0.891, 1.098	0.8380	0.987	0.776, 1.254	0.9129	0.863	0.594, 1.254	0.4389

Year of entry was adjusted in the analyses
CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy.

Table 3-2. Hazard ratios for development of cancers: multivariate analyses

	Colorectal			Hepatobiliary			Pancreas		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
HRT									
No	1.000			1.000			1.000		
Yes	0.757	0.577, 0.995	0.0457	0.847	0.606, 1.186	0.3336	1.163	0.674, 2.008	0.5872
Age (Years)									
40-49	1.000			1.000			1.000		
50-59	1.795	1.253, 2.571	0.0014	3.102	1.850, 5.201	<.0001	1.945	0.790, 4.785	0.1476
60-69	2.640	1.738, 4.011	<.0001	3.794	2.139, 6.728	<.0001	4.355	1.633, 11.614	0.0033
70~	6.244	4.036, 9.661	<.0001	8.614	4.800, 15.458	<.0001	12.579	4.772, 33.158	<.0001
Income level									
-30% (low)	1.000			1.000			1.000		
31-60%	1.084	0.853, 1.377	0.5104	0.912	0.676, 1.232	0.5486	0.847	0.465, 1.543	0.5873
61-90%	0.994	0.766, 1.289	0.9621	0.832	0.599, 1.155	0.2716	1.323	0.747, 2.345	0.3373
+91% (high)	1.002	0.753, 1.333	0.9907	0.816	0.567, 1.173	0.2714	1.222	0.657, 2.275	0.5265
Region									
Metropolitan	1.000			1.000			1.000		
Others	0.793	0.658, 0.955	0.0147	1.026	0.810, 1.301	0.8291	0.712	0.462, 1.096	0.1228
Charlson comorbidity index									
1	1.000			1.000			1.000		
2	0.966	0.631, 1.479	0.8737	0.846	0.449, 1.594	0.6047	1.165	0.384, 3.538	0.7874
3	1.212	0.765, 1.922	0.4130	1.211	0.624, 2.348	0.5714	1.414	0.440, 4.552	0.5609
4+	0.980	0.656, 1.464	0.9212	1.269	0.699, 2.303	0.4345	1.334	0.469, 3.794	0.5887

Year of entry was adjusted in the analyses
CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy.

Table 4-1. Hazard ratios for development of cancers: subgroup analyses according to HRT regimen

		Any cancer			GI			Gastric		
	N (%)	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
HRT type										
Estradiol*	9,125 (40.42)	1.064	0.944, 1.199	0.3082	0.823	0.631, 1.072	0.1485	0.742	0.473, 1.164	0.1943
Conjugated estrogen*	2,147 (9.51)	1.154	0.953, 1.397	0.1417	0.984	0.675, 1.435	0.9343	0.895	0.461, 1.738	0.7436
Tibolone	6,102 (27.03)	1.093	0.958, 1.247	0.1844	0.817	0.627, 1.066	0.1364	0.891	0.579, 1.371	0.5987
Mixed	5,203 (23.05)	0.949	0.823, 1.095	0.4733	0.689	0.498, 0.952	0.0242	0.669	0.392, 1.142	0.1405
Combination†										
Estrogen only regimen	4,566 (20.22)	1.258	1.092, 1.450	0.0015	1.037	0.772, 1.394	0.8076	0.736	0.414, 1.307	0.2952
Combination regimen	6,575 (29.12)	0.958	0.831, 1.105	0.5593	0.728	0.531, 0.998	0.0488	0.821	0.505, 1.335	0.4265
Mixed	4,467 (19.79)	0.892	0.759, 1.049	0.1662	0.722	0.508, 1.027	0.0700	0.647	0.355, 1.179	0.1549

Other covariates (age group, income, region, Charlson comorbidity index, and year of study entry) were adjusted in each survival analysis

CI, confidence interval; DDD, defined daily dose; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy.

*included combination regimens

†except for 6,969 persons taking tibolone alone

Table 4-2. Hazard ratios for development of cancers: subgroup analyses according to HRT regimen

		Colorectal			Hepatobiliary			Pancreas		
	N (%)	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
HRT type										
Estradiol*	9,125 (40.42)	0.754	0.475, 1.197	0.2312	1.023	0.596, 1.758	0.9797	1.253	0.503, 3.119	0.6279
Conjugated estrogen*	2,147 (9.51)	0.926	0.477, 1.798	0.8198	0.915	0.405, 2.065	0.8302	2.141	0.773, 5.931	0.1433
Tibolone	6,102 (27.03)	0.716	0.446, 1.151	0.1680	0.838	0.478, 1.468	0.5361	0.818	0.297, 2.252	0.6975
Mixed	5,203 (23.05)	0.731	0.428, 1.248	0.2502	0.611	0.288, 0.299	0.2005	0.998	0.312, 3.189	0.9967
Combination†										
Estrogen only regimen	4,566 (20.22)	1.094	0.673, 1.781	0.7162	1.070	0.567, 2.017	0.8350	2.536	1.161, 5.541	0.0196
Combination regimen	6,575 (29.12)	0.566	0.310, 1.031	0.0627	0.900	0.478, 1.697	0.7455	0.641	0.157, 2.619	0.5353
Mixed	4,467 (19.79)	0.776	0.436, 1.380	0.3873	0.668	0.297, 1.506	0.3307	1.268	0.396, 4.055	0.6891

Other covariates (age group, income, region, Charlson comorbidity index, and year of study entry) were adjusted in each survival analysis

CI, confidence interval; DDD, defined daily dose; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy.

*included combination regimens

†except for 6,969 persons taking tibolone alone

Table 5-1. Hazard ratios for development of cancers: subgroup analyses according to baseline characteristics

	Any cancer			GI			Gastric		
	HR*	95% CI	*p* value	HR*	95% CI	*p* value	HR*	95% CI	*p* value
Age at HRT									
40-49	0.996	0.882, 1.124	0.9440	0.948	0.709, 1.269	0.7214	1.121	0.736, 1.707	0.5948
50-59	1.030	0.919, 1.155	0.6081	0.657	0.509, 0.846	0.0011	0.654	0.427, 1.002	0.0511
≥60	1.224	1.030, 1.455	0.0217	0.923	0.699, 1.220	0.5740	0.671	0.384, 1.173	0.1617
Income level									
-30% (low)	1.012	0.885, 1.156	0.8633	0.747	0.557, 1.000	0.0498	0.624	0.371, 1.050	0.0758
31-60%	1.033	0.895, 1.191	0.6581	0.763	0.569, 1.023	0.0703	0.807	0.502, 1.295	0.3739
61-90%	1.009	0.865, 1.177	0.9097	0.785	0.564, 1.093	0.1511	0.785	0.454, 1.356	0.3851
+91% (high)	1.249	1.044, 1.495	0.0150	1.048	0.734, 1.496	0.7972	1.071	0.599, 1.915	0.8169
Region									
Metropolitan	1.064	0.958, 1.182	0.2470	0.728	0.580, 0.915	0.0065	0.767	0.528, 1.115	0.1648
Others	1.040	0.935, 1.157	0.4717	0.896	0.722, 1.113	0.3214	0.808	0.559, 1.168	0.2569
CCI									
1	0.918	0.793, 1.062	0.2501	0.832	0.583, 1.187	0.3105	1.023	0.622, 1.683	0.9283
2	1.075	0.948, 1.219	0.2574	0.706	0.529, 0.941	0.0174	0.704	0.444, 1.115	0.1348
3	0.977	0.806, 1.184	0.8106	0.734	0.512, 1.050	0.0907	0.710	0.376, 1.344	0.2934
4+	1.260	1.078, 1.472	0.0036	0.971	0.734, 1.286	0.8382	0.786	0.450, 1.372	0.3970

Other covariates were adjusted in each survival analysis
CCI, Charlson comorbidity index; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy
*Hazard ratios for cancer development in HRT users compared to non-users

Table 5-2. Hazard ratios for development of cancers: subgroup analyses according to baseline characteristics

	Colorectal			Hepatobiliary			Pancreas		
	HR*	95% CI	*p* value	HR*	95% CI	*p* value	HR*	95% CI	*p* value
Age at HRT									
40-49	0.722	0.426, 1.225	0.2276	0.920	0.429, 1.971	0.8293	1.794	0.569, 5.659	0.3188
50-59	0.678	0.442, 1.041	0.0754	0.752	0.457, 1.237	0.2618	0.330	0.079, 1.385	0.1299
≥60	0.898	0.557, 1.448	0.6599	0.905	0.512, 1.600	0.7309	1.875	0.904, 3.889	0.0913
Income level									
-30% (low)	0.667	0.395, 1.126	0.1297	0.920	0.520, 1.628	0.7748	1.192	0.447, 3.178	0.7249
31-60%	0.625	0.371, 1.053	0.0777	0.777	0.411, 1.468	0.4369	1.789	0.641, 4.989	0.2664
61-90%	0.858	0.495, 1.488	0.5863	0.644	0.292, 1.419	0.2748	1.060	0.359, 3.131	0.9160
+91% (high)	1.082	0.593, 1.973	0.7979	1.079	0.499, 2.332	0.8467	0.718	0.163, 3.165	0.6620
Region									
Metropolitan	0.593	0.394, 0.892	0.0120	0.808	0.491, 1.331	0.4035	1.182	0.569, 2.453	0.6542
Others	0.958	0.663, 1.384	0.8182	0.883	0.560, 1.391	0.5914	1.157	0.508, 2.633	0.7284
CCI									
1	0.631	0.326, 1.223	0.1726	0.803	0.310, 2.080	0.6513	1.178	0.250, 5.548	0.8362
2	0.852	0.539, 1.346	0.4921	0.714	0.378, 1.351	0.3012	NA	-	0.9874
3	0.688	0.374, 1.268	0.2308	0.422	0.168, 1.059	0.0662	3.061	1.162, 8.063	0.0235
4+	0.766	0.455, 1.291	0.3176	1.280	0.778, 2.104	0.3310	1.418	0.618, 3.252	0.4093

Other covariates were adjusted in each survival analysis
CCI, Charlson comorbidity index; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy
*Hazard ratios for cancer development in HRT users compared to non-users

6. Hormone replacement therapy and mortality

Kaplan-Meier survival curves regarding mortality are shown in Figure 3. All-cause mortality were lower in HRT users than non-users (p<0.0001), while cancer-related mortality was not significantly associated with HRT. However, mortality from GI cancer was lower in HRT users than non-users (p=0.0377). Table 6 shows survival analyses using Cox proportional hazard models to determine the relationship between HRT use and mortality. The model includes age group, income level, region, CCI score, and year of study entry. In this multivariate analysis, all-cause mortality was lower in HRT users than in non-users (HR, 0.784; p<.0001), whereas cancer-related mortality was not different between the groups. Also, mortality from GI cancer was lower in HRT users compared to non-users (HR, 0.737; p=0.0445), which we attributed to GC and CRC mortality (HR, 0.411 and HR, 0.181, respectively).

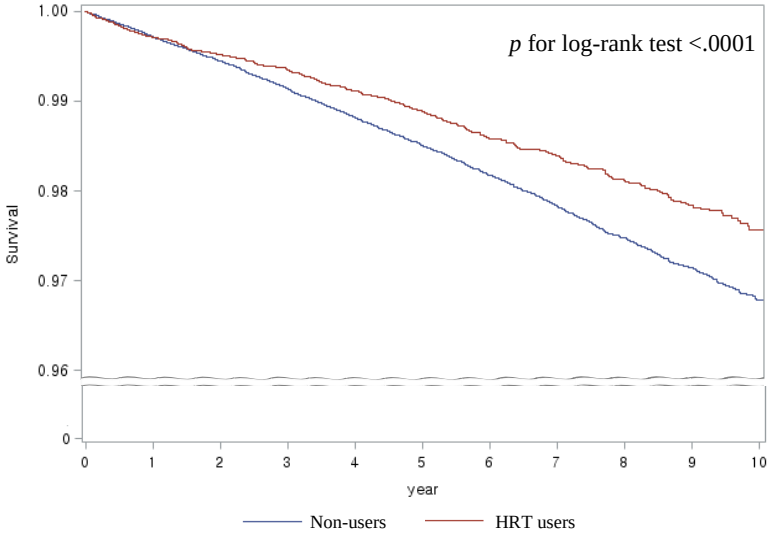

Figure 3-1. Kaplan-Meier survival curves for all-cause mortality

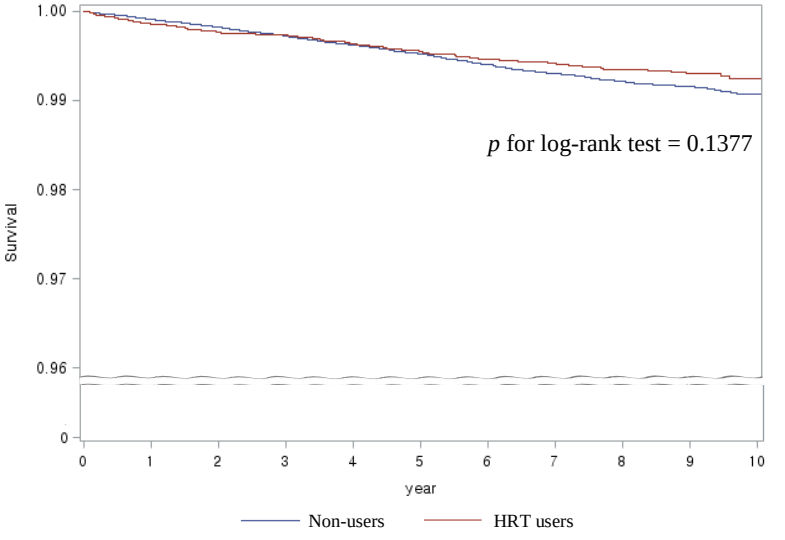

Figure 3-2. Kaplan-Meier survival curves for cancer-related mortality

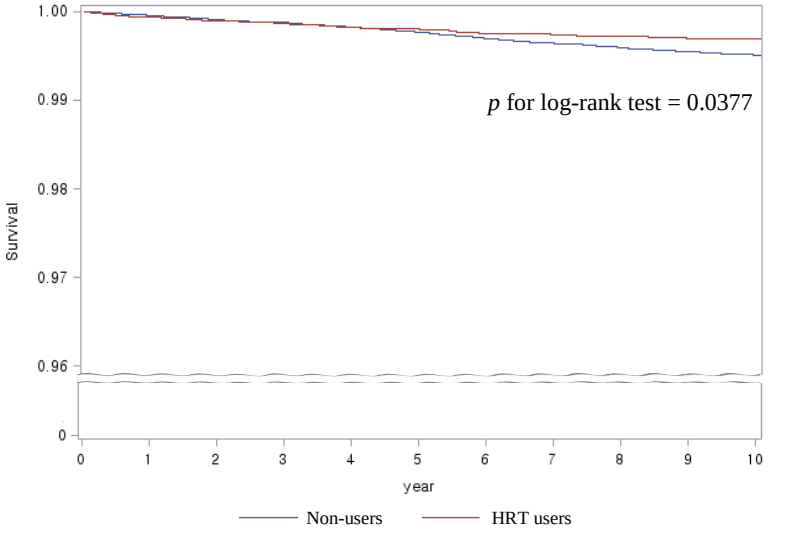

Figure 3-3. Kaplan-Meier survival curves for gastrointestinal cancer mortality

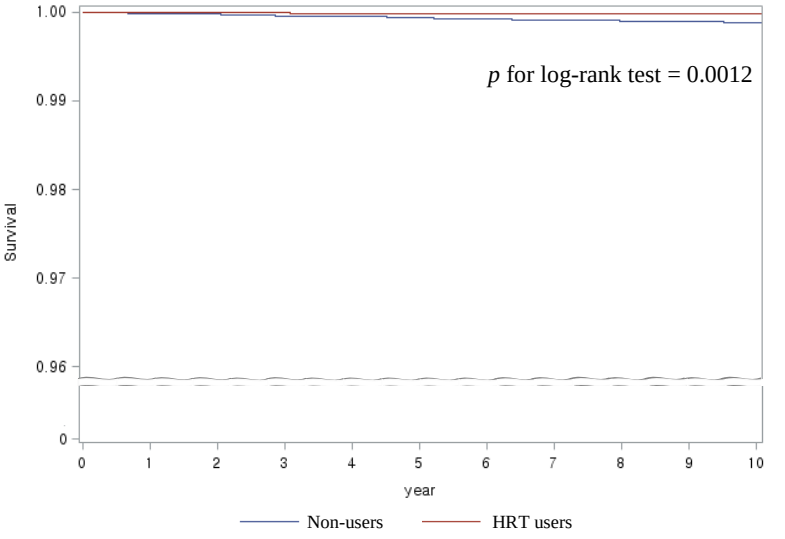

Figure 3-4. Kaplan-Meier survival curves for colorectal cancer mortality

Table 6. Hazard ratios for mortality: multivariate analyses

Outcome variables	HRT users*		Non-users*		HR†	95% CI	*p* value
	N	rate	N	rate			
All-cause mortality	333	0.238	2,173	0.314	0.784	0.698, 0.880	<.0001
Cancer-related mortality	115	0.082	661	0.096	0.874	0.717, 1.066	0.1843
Mortality from GI cancer	50	0.036	338	0.049	0.737	0.547, 0.993	0.0445
Gastric	7	0.005	86	0.012	0.411	0.190, 0.890	0.0240
Colorectal	3	0.002	81	0.012	0.181	0.057, 0.572	0.0036
Hepatobiliary	26	0.019	121	0.018	1.077	0.704, 1.647	0.7332
Pancreatic	13	0.009	48	0.007	1.333	0.721, 2.463	0.3598

Other covariates (age group, income, region, Charlson comorbidity index, and year of study entry) were adjusted in each survival analysis
CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy
*Mortality rates per 100,000 person-years
†Adjusted hazard ratios for mortality in HRT users compared to non-users

7. Dose-response relationship

We performed Landmark analysis for subgroup analyses by HRT dose, which included 19,543 HRT users and 96,548 non-users. Figure 4 shows the survival curves according to HRT dose. The DDD increased from 1 to 4, with 4 indicating 600 or more of HRT dose. Log rank *p* values by increasing dose for GI cancer and CRC were 0.0040 and 0.0896, respectively. The log rank test was not significant in terms of GC and HRT dose (*p*=0.2146). Table 7 indicates the rate of incidence and mortality of cancers according to HRT dose using Landmark analysis. The incidence of GI cancer was negatively associated with HRT dose (HR, 0.79, 0.71, 0.49, and 0.55 respectively, *p* for trend=0.0002). Also, CRC diagnosis in HRT users compared to non-users decreased to 0.84, 0.64, 0.63, and 0.15 as HRT dose increased from less than 100 to over 600 of DDD (*p* for trend=0.0069). Hazard ratios for all-cause mortality in HRT users compared to non-users were 0.76, 0.88, 0.64, and 0.34 as HRT dose increased (*p* for trend<0.0001). *P* for trend was significant in cancer-related mortality and GI cancer mortality (0.0052 and 0.0064, respectively), whereas it was not associated with other cancer mortality.

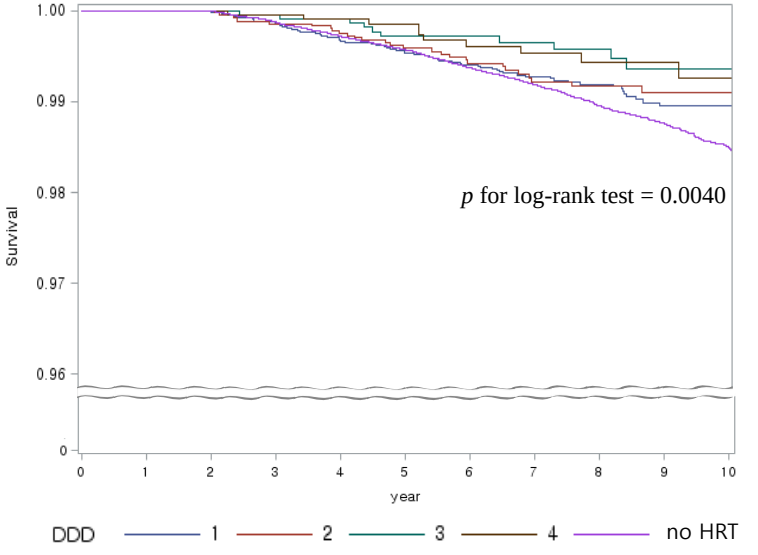

Figure 4-1. Kaplan-Meier survival curves for gastrointestinal cancer incidence: dose-response relationship. DDD, defined daily dose. 5 groups were based on DDD of HRT (1, ≤100; 2, 100~300; 3; 300~600; 4, ≥600; and no HRT)

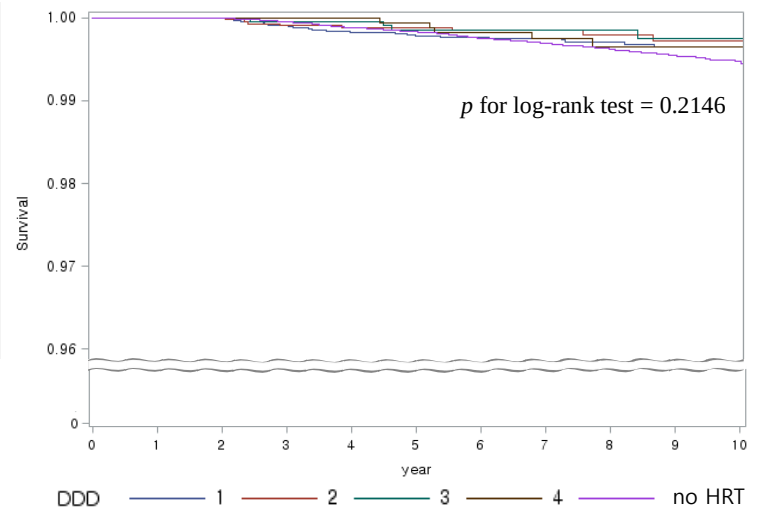

Figure 4-2. Kaplan-Meier survival curves for gastric cancer incidence: dose-response relationship. DDD, defined daily dose. 5 groups were based on DDD of HRT (1, ≤100; 2, 100~300; 3; 300~600; 4, ≥600; and no HRT)

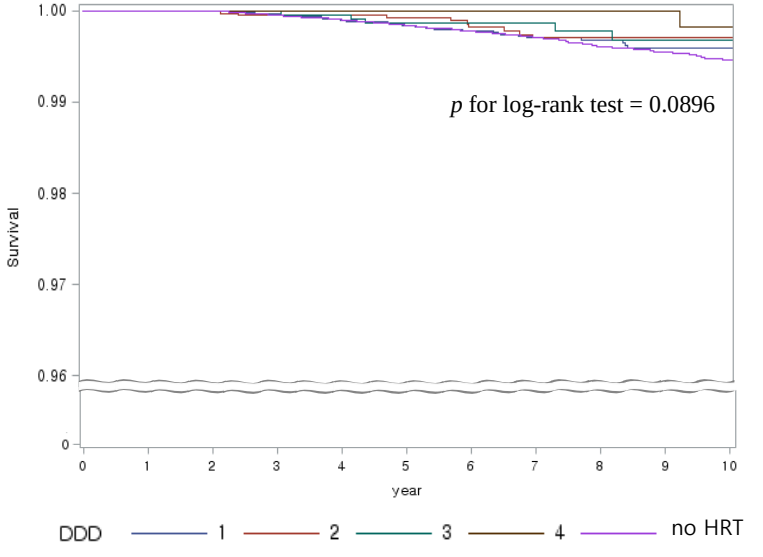

Figure 4-3. Kaplan-Meier survival curves for colorectal cancer incidence: dose-response relationship. DDD, defined daily dose. 5 groups were based on DDD of HRT (1, ≤100; 2, 100~300; 3; 300~600; 4, ≥600; and no HRT)

Table 7-1. Hazard ratios for cancer incidence and mortality by HRT dose*

			Any cancer			GI			Gastric		
		N	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Incidence											
DDD	no HRT	96,548	1.000	-	0.4709†	1.000	-	0.0002†	1.000	-	0.0223†
	≤100	10,199	1.004	0.893, 1.128	0.9503	0.786	0.617, 1.002	0.0520	0.790	0.529, 1.180	0.2494
	100~300	4,423	0.957	0.803, 1.139	0.6189	0.710	0.487, 1.035	0.0746	0.553	0.274, 1.116	0.0982
	300~600	2,569	1.031	0.827, 1.284	0.7886	0.488	0.269, 0.884	0.0180	0.476	0.178, 1.278	0.1408
	≥600	2,352	0.876	0.681, 1.127	0.3031	0.545	0.292, 1.018	0.0568	0.709	0.293, 1.719	0.4471
Mortality											
DDD	no HRT	96,548	1.000	-	0.0052†	1.000	-	0.0064†	1.000	-	0.0264†
	≤100	10,199	0.663	0.470, 0.936	0.0194	0.514	0.300, 0.881	0.0156	0.445	0.139, 1.421	0.1718
	100~300	4,423	0.891	0.563, 1.410	0.6224	0.798	0.410, 1.553	0.5067	NA‡	-	-
	300~600	2,569	0.852	0.455, 1.595	0.6165	0.481	0.154, 1.503	0.2081	NA‡	-	-
	≥600	2,352	0.113	0.016, 0.803	0.0294	0.213	0.030, 1.521	0.1232	NA‡	-	-

Other covariates (age group, income, region, Charlson comorbidity index, and year of study entry) were adjusted in each survival analysis
CI, confidence interval; DDD, defined daily dose; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy; NA, not available.
*Using Landmark analysis (19,543 HRT users vs. 96,548 non-users)
†*p* for trend
‡There was no death from gastric cancer at the HRT dose.

Table 7-2. Hazard ratios for cancer incidence and mortality by HRT dose*

			Colorectal			Hepatobiliary			Pancreas		
		N	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Incidence											
DDD	no HRT	96,548	1.000		0.0069†	1.000		0.1765†	1.000		0.6680†
	≤100	10,199	0.843	0.568, 1.251	0.3970	0.639	0.355, 1.148	0.1338	0.825	0.330, 2.065	0.6813
	100~300	4,423	0.643	0.331, 1.249	0.1926	0.866	0.407, 1.845	0.7095	1.538	0.556, 4.252	0.4065
	300~600	2,569	0.626	0.258, 1.515	0.2988	0.443	0.110, 1.787	0.2527	NA‡	-	-
	≥600	2,352	0.152	0.021, 1.082	0.0600	0.874	0.278, 2.743	0.8174	0.904	0.125, 6.558	0.9203
Mortality											
DDD	no HRT	96,548	1.000		0.0672†	1.000		0.3329†	1.000		0.8495†
	≤100	10,199	NA§	-	-	0.612	0.267, 1.403	0.2464	0.963	0.343, 2.705	0.9429
	100~300	4,423	NA§	-	-	1.476	0.644, 3.380	0.3574	1.666	2.705, 5.411	0.3957
	300~600	2,569	1.403	0.341, 5.762	0.6387	NA§	-	-	NA§	-	-
	≥600	2,352	NA§	-	-	0.633	0.088, 4.566	0.6505	NA§	-	-

Other covariates (age group, income, region, Charlson comorbidity index, and year of study entry) were adjusted in each survival analysis
CI, confidence interval; DDD, defined daily dose; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy; NA, not available.
*Using Landmark analysis (19,543 HRT users vs. 96,548 non-users)
†*p* for trend
‡There was no pancreatic cancer detected at the HRT dose.
§There was no death from each cancer at the HRT dose.

8. Sensitivity analysis

Next, we performed sensitivity analysis on the main outcomes using the data set included in the Landmark analysis (n=116,091) (Table 8). The incidence rate of GI cancer was significantly lower in HRT users than in non-users (0.086 vs. 0.121, HR, 0.703; *p*=0.0003). Hazard ratios for colorectal cancer was also lower in HRT users than non-users (HR, 0.693; *p*=0.0266). These results were comparable to the results of the entire data set (n=133,690). Gastric cancer diagnosis, which showed marginal significance in the entire data set, was significantly lower in HRT users compared to non-users (0.031 vs. 0,044, HR, 0.684; *p*=0.0202). In addition, hepatobiliary or pancreatic cancer was not associated with HRT use in this sensitivity analysis.

Table 8. Sensitivity analyses of cancer incidence using Landmark data set

Outcome variables	HRT users*		Non-users*		HR†	95% CI	*p* value
	N	rate*	N	rate*			
Any cancer	591	0.422	2,960	0.428	0.981	0.898, 1.072	0.6792
GI cancer	120	0.086	836	0.121	0.703	0.580, 0.852	0.0003
Esophageal	0	0.000	4	0.001	-	-	0.9977
Gastric	43	0.031	303	0.044	0.684	0.497, 0.943	0.0202
Colorectal	42	0.030	297	0.043	0.693	0.502, 0.958	0.0266
Hepatobiliary	24	0.017	174	0.025	0.689	0.449, 1.057	0.0883
Pancreatic	10	0.007	55	0.008	0.89	0.453, 1.748	0.7341

Other covariates (age group, income, region, Charlson comorbidity index, and year of study entry) were adjusted in each survival analysis

CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; HRT, hormone replacement therapy

*Incidence rates per 100,000 person-years

†Adjusted hazard ratios for cancer incidence in HRT users compared to non-users

IV. DISCUSSION

The rate of GI cancer diagnosis was 0.155 per 100,000 person-years in 831,311 nationwide women's sample cohort during median follow-up of 79.6 months. It was lower in HRT users compared to non-users (0.13 vs. 0.16, log-rank *p*=0.0089). The rate of GC and CRC diagnosis was marginally lower in HRT users compared to non-users (*p*=0.0887 and *p*=0.0517), whereas those of hepatobiliary or pancreatic cancer did not differ between HRT users and non-users. In the multivariate analyses, HRT use was significantly related with

decreased diagnosis of GI cancer and CRC (HR, 0.81; *p*=0.0081 and HR, 0.76; *p*=0.0457), and GC diagnosis was marginally related with HRT use (HR, 0.79; *p*=0.0733). Mortality from GI cancer was lower in HRT users than non-users (HR, 0.737; *p*=0.0445), which we attributed to GC and CRC mortality (HR, 0.411; *p*=0.0240 and HR, 0.181; *p*=0.0036). These associations of HRT with GI cancer incidence or mortality showed a dose-response relationship. All-cause mortality as well as mortality from GI cancer, GC, or CRC was significantly lowered in HRT users than non-users (HR, 0.78, 0.74, 0.41, and 0.18, respectively).

The higher rate of incidence of GI cancer in men than in women and the gradually increasing rate of incidence after menopause in women suggests a protective role of female hormones against GI cancer. Many clinical studies have supported this by showing lower risk of CRC in HRT users.[8-12] The effect of HRT on CRC carcinogenesis is known to be related to estrogen receptor beta (ERβ) [6,7,21]. The ERβ mediated mechanism may be involved in the effect of HRT on other GI cancers. Further research about the association between ERβ and intestinal carcinogenesis is warranted. A recent study of CRC patients demonstrated that high ERβ expression decreases the risk of morality and cancer recurrence [22], consistent with our findings regarding mortality of CRC. However, there is controversy as to whether HRT has a positive effect on CRC prognosis and mortality [23]. It has been asserted that the protective effect of estrogen is limited to the initiation of CRC; once the cancer is developed, estrogen increases proliferation of the disease. This is supported by an RCT that reported a decrease in the risk of CRC that later increased the cumulative hazard of death from CRC in HRT users [8,24]. If so, regular colonoscopy screening may be needed in women using HRT. It is desirable to select an appropriate duration for HRT, taking into consideration the effects of HRT on other diseases as well as intestinal carcinogenesis. In addition, we need to perform further research that extends the observation period.

Only nine esophageal cancers were detected during the entire study period. A previous population based cohort study and a nested case control study found that HRT use is significantly related to decreased esophageal cancer risk, reporting OR=0.62 and RR=0.68 respectively [16,17]. As esophageal cancer is a very rare disease in South Korea, especially among women, it was impossible to evaluate the association with HRT use in this cohort design. Hazard ratios for GC diagnosis was 0.787 in our study. Female hormones can generally affect

intestinal carcinogenesis and may provide a protective effect against not only CRC but also GC. Several Western studies showed different results in terms of GC [16,17,25]. Our findings support previous claims of the protective effect of HRT on GC, which was meaningful because it was conducted in South Korea, where the prevalence of GC is high. There have been few studies of the remaining GI cancers. Hepatobiliary and pancreatic caners are different biologically from other GI cancers that originate in hollow viscus. This may explain why we found that HRT did not affect hepatobiliary or pancreatic cancers. In a recent large prescription-based cohort study in Sweden, HRT significantly decreased the standardized incidence ratio (SIR) of liver cancer compared to the background population, while it was not associated with biliary and pancreatic cancers. An additional matching cohort design using the same data of HRT users in Sweden found significantly decreased incidence of pancreatic cancer in HRT users compared with matched controls (OR=0.77) [26]. Our result showed increased HR of pancreatic cancer risk, even though statistical power was insufficient. Especially, the rate of pancreatic cancer diagnosis was significantly increased in the HRT users with only estrogen. Hazard ratio for a diagnosis of any-type cancer was also increased in those with only estrogen. It is needed to consider associations of HRT with other cancers besides GI cancer. Meanwhile, the median follow-up period was about 6.6 years in our study, not enough to investigate cancer incidence. As shown in Figure 2, the survival curves between HRT users and non-users showed clear differences after the middle of the follow-up period in most GI cancers. Thus, a study with a longer observation period may allow more favorable results demonstrating HRT's effect on GI cancer risks.

We examined only the relationship between HRT and GI cancers among effects of HRT on various diseases. Well-known example is the negative aspect of HRT, such as increased risk of breast cancer [27]. Thus, the generalization of our findings to policies that encourage HRT use should be considered with caution. According to previous studies regarding breast cancer and HRT, the longer HRT is used, the greater the risk of breast cancer [28,29]. However, there is no suggested duration of HRT use without increasing the risk of breast cancer. In our study, GI cancer incidence decreased when using HRT for over two years. Additional studies to evaluate whether the use of HRT for over two years affects breast cancer development would be useful. A randomized trial demonstrated that early HRT users were significantly less likely than non-users to develop cardiovascular disease (CVD) [30]. They also found decreased mortality related

with CVD in HRT users. The lower all-cause mortality rate in HRT users in our study may be due to the effect of HRT on other diseases including CVD. Recommendation of HRT use should be made individually considering the characteristics of each postmenopausal woman. A total duration of HRT use should be determined considering risk-benefits of HRT in the individual.

This study has some strength. First, whether HRT can reduce GI cancer is an area of interest in the West and has been actively studied. However, there is no large-scale study conducted in the East. This is the first nationwide cohort study in Asia. Second, by using samples from the NHIS claim data for the entire population, study subjects represented the general population of South Korea. Third, we used Landmark analysis to determine the dose-response relationship of HRT with cancer development to minimize the possibility of lead time bias. Finally, this study was one of few studies to include all GI cancers, and we analyzed the effects of HRT on mortality as well as incidence of GI cancers.

This study has some limitations. First, we used prescription codes of claim data, thus, the study may not exactly coincide with actual HRT intake in individuals, especially for women who received HRT once or for a short duration. Also, it cannot be asserted that almost all regimens included in the study were prescribed for HRT purposes only, even though the indications include postmenopausal symptoms. Second, for the investigation of rare GI cancers such as esophageal, hepatobiliary, or pancreatic cancer, this study was limited by the small sample size, even though we used a large database. In relation to the study design, there are limitations with time of the study entry and follow-up period. Before the study entry, both HRT users and non-users were not taking HRT and the period was not considered in the study. Thus, there may be bias related to the actual follow-up period in both groups. Third, we could not adjust important risk factors for GI cancers such as environmental factors or family history, which may be considerable confounders. However, we considered the factors affecting health outcomes by adjusting CCI scores based on various chronic diseases. Finally, because data relating to cancer stage and treatment was not available in our data, there may be controversy about comparing mortality rates. Further analysis, including data of national cancer registry, is required in the future.

V. CONCLUSION

In this study postmenopausal HRT was associated with decreased diagnosis of GI cancer, especially for CRC and GC, in women. Furthermore, HRT use was significantly associated with decreased mortality from GI cancer. These negative associations of HRT with GI cancer showed a dose-response relationship. This study supports previous research that demonstrates the protective effect of HRT on GI cancer. Our findings based on national sample data provide evidence of the need for research on the entire population.

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ABSTRACT (IN KOREAN)

폐경기 호르몬 대체요법이 소화기암 발생에 미치는 영향, 공단 자료를 이용한 코호트 연구

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배경: 여성 호르몬은 장 발암과정 (intestinal carcinogenesis)을 억제하는 효과가 있는 것으로 알려져 있다. 이에 따라 폐경기 호르몬 대체요법과 대장암 발생에 관한 많은 임상 연구들이 보고되었지만, 동양에서 시행된 연구는 드물다. 이 연구의 목적은 우리나라에서 호르몬 대체요법이 소화기암에 미치는 영향을 알아보고, 이에 대한 용량-반응 관계를 확인하고자 하였다.

방법: 국민건강보험공단 청구자료의 표본 데이터를 사용 하였다. 디자인은 성향 점수 (propensity score)를 이용한 매칭 코호트 연구로, 총 133,690명이 연구에 포함되었다. 2004년부터 2013년 사이에 호르몬 대체요법을 시행한 여성 22,577명과 이에 대한 1:5 매칭 대조군 111,113명을 대상으로 소화기암 발생률과 사망률을 비교하였다. 통계 분석은 카플란-마이어 (Kaplan-Meier) 생존 분석과 Cox 비례위험모형을 이용하였다. 모형은 나이, 거주지, 소득 수준, 동반질환 지수 (Charlson comorbidity index), 코호트에 등록된 연도를 포함하였다. 여성호르몬의 종류와 용량에 따른 하위그룹분석을 시행하였고, 용량-반응 관계는 Landmark 분석을 사용하였다.

결과: 추적 기간은 중앙값 79.6개월이었다. 소화기암 발생률은

호르몬 복용군과 대조군에서 각각 100,000인년 당 0.13과 0.16이었다. 카플란-마이어 생존 곡선에서 호르몬 대체요법을 한 경우 대조군에 비해 유의하게 소화기암 발생률이 낮았고 (P=0.0089), 위암과 대장암 발생률 역시 호르몬 복용군에서 낮은 경향이 있었다 (P=0.0887 및 P=0.0517). Cox 비례위험모형을 이용한 다변량 분석에서, 호르몬 복용군에서 소화기암 및 대장암 발생률이 낮았고 (HR, 0.809; P=0.0081 및 HR, 0.757; P=0.0457), 이는 호르몬 용량이 증가할수록 뚜렷하였다 (P for trend, 0.0002 및 0.0069). 위암 발생률은 호르몬 복용군에서 감소하는 경향을 보였고 (HR, 0.787; P=0.0733), 간담도암과 췌장암의 경우 연관성이 없었다. 또한 호르몬 복용군에서 대조군에 비해 소화기암 사망률이 유의하게 낮았다 (HR, 0.737; P=0.0445).

결론: 한국에서 폐경기 여성의 호르몬 대체요법은 소화기암 발생률 감소와 유의한 관련성이 있었으며, 특히 대장암에 뚜렷하였다. 또한 이 연관성에 대해 용량-반응 관계가 있음을 확인하였다.

핵심되는 말: 호르몬 대체요법, 소화기암, 대장암, 생존 분석