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Original Article

Descriptive Analysis of Gastric Cancer Mortality in Korea, 2000-2020

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Purpose This study aimed to examine secular trends, age-period-cohort effects, and geographical differences in gastric cancer (GC) mortality in Korea.

Materials and Methods Using cause of death data from the Korean Statistical Information Service for GC from 2000 to 2020, we calculated average annual percentage changes (AAPCs) in the age-standardized mortality of GC in 17 cities and provinces through joinpoint regression. Decomposition of age, period, and cohort effects on GC mortality were elucidated by applying a log-linear model and an intrinsic estimate method. Spatial patterns and the degree of spatial clustering in 250 administrative regions were explored via Moran's I statistics. Stratification by sex was performed for all analyses.

Results The age-standardized mortality of GC per 100,000 persons declined from 29.0 in 2000 to 7.9 in 2020 (AAPC, –6.28%). Age-period-cohort analyses of GC mortality showed a downward trend among 5-year age groups from age 20-89 years across five-year periods from 2005-2020 and 5-year birth cohorts from 1920 to 2000. Overall, the younger birth cohort showed lower mortality rates than the older cohort within the same period. In 2020, clusters of high GC mortality were observed in the central area for men (Chungcheongbuk-do, Jeollabuk-do, Gyeongsangbuk-do, and Gyeongsangnam-do) and in the eastern area for women (Gyeongsangbuk-do).

Conclusion This study identified a downward trend in GC mortality among men and women from 2000 to 2020 in Korea. This trend was mainly attributed to birth cohort rather than period effects. Spatial analysis showed high GC mortality in the Chungcheong-do and Gyeongsangbuk-do areas.

Key words Joinpoint regression, Age-period-cohort analysis, Spatial analysis, Gastric cancer mortality, Korea

Introduction

According to Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2020, gastric cancer remains the fourth leading cause of cancer deaths worldwide, with an estimated 768,793 deaths [1]. Data from GLOBOCAN 2020 and the World Health Organization Mortality Database for 48 countries reported declines in gastric cancer mortality for men of 41 countries and women of 39 countries; of these countries, 25 and 23 countries were in Europe, respectively [2].

Despite the high incidence of gastric cancer, screening to detect precursor tumors at an early stage contributed to a relatively higher 5-year survival rate in Korea (71.5%) and Japan (65.0%) than in other areas (20%) [3]. In Korea, the Korean National Cancer Screening Program (NCSP) was launched in 1999 and recommends that people aged 40 years and older undergo biennial upper endoscopy or upper gastrointestinal series (UGIS) [4]. Since 2018, endoscopy has been recommended as the primary form of gastric cancer screening [5]. Overall, approximately 50% of the reduction in gastric cancer mortality was attributable to endoscopies and not UGIS, especially in people aged over 50 years [4,6].

The age-standardized gastric cancer mortality rate has decreased in recent years [7], whereas decomposing the contribution of age, calendar period, and birth cohort may be beneficial for understanding the reasons for the trends in gastric cancer mortality [8]. Age exerts the cumulative effects of multiple age- and lifestyle-related factors and changes due to natural physical deterioration [8]. Period effects exert the influence of external factors on all age groups, while cohort effects have an impact on the unique exposure of a group of individuals at different times [8].

A previous study reported a national downward trend, which was explained by the birth cohort effect, for gastric cancer mortality during 1983-2013 [9]. However, the mortality for the 2003-2013 period was estimated based on the trends in preceding years from 1983 to 2002 [9]. Another study using data from the National Statistical Office confirmed the main explanation of the cohort effect on the downward mortality trend of gastric cancer during 1983-2012 [10]. Given that the

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research period did not cover the long term after the implementation of the NCSP, the contribution of the period effect remained unclear [10].

Although gastric cancer mortality has been declining in recent decades, considerable geographical variations have been reported in several countries [11-14]. In the United States, regional differences in gastric cancer mortality were attributed to living in rural areas, diabetes prevalence, and percentages of ever smokers [15]. While in Korea, the geographical disparities in gastric cancer mortality have been attributed to differences in socioeconomic status, lifestyle factors, and cardiometabolic diseases [16-19]. Moreover, health care access may also contribute to this variation; only an estimated 62% of cancer patients in Korea are treated in hospitals with high-level facilities and treatments [20]. Rural dwellers may thus be more vulnerable to emergency situations than those who live in urban areas or metropolitan cities and provinces [20]. According to the Korea Statistics, the age-standardized gastric cancer mortality in 2000 was from 25.1 (for Seoul) to 35.2 (for Chungcheongnam-do) per 100,000 persons [21]. Until 2020, there rates declined to 9.2 (for Seoul) and 7.5 (for Chungcheongnam-do) per 100,000 persons [21]. In the perspective of health policy makers, understanding geographical differences in gastric cancer mortality may be helpful in determining priorities and deciding interventions for disease control.

Therefore, we carried out a trend analysis to assess temporal trends of gastric cancer mortality in Korea during 2000-2020. We then used an age-period-cohort model to examine the separate effects of age, period, and cohort on gastric cancer mortality over the research period. Finally, we conducted a spatial analysis to identify spatial clusters of gastric cancer mortality across Korea.

Materials and Methods

1. Data source and study area

In this study, we extracted national-level data on cause of death from Statistics Korea through the Korean Statistical Information Service (KOSIS) [21]. Data on gastric cancer were defined using International Classification of Diseases, 10th revision code C16. Age-standardized rates at the national level and for 17 metropolitan cities and provinces were collected, with the standard mid-year population in Korea for 2005, for the secular trend analysis.

For the age-period-cohort analysis, we grouped the number of gastric cancer deaths and total individuals by age group for each year from 2000 to 2020.

The age-standardized mortality rates of gastric cancer in approximately 250 municipal regions during 2000-2020 were obtained for geographical disparity analysis. The shapefile map at the municipal level of 250 districts in Korea was obtained from the Korea Geographic Information System (GIS) developer to visualize the regional rates.

To calculate the participation rates of gastric cancer screening, we obtained the number of eligible persons for screening and the number of screening participants between 2010 and 2019.

2. Statistical analysis

First, we conducted joinpoint regression analysis to explore the trends of gastric cancer mortality at the national and provincial levels. Although annual gastric cancer mortality data were available for 250 administrative regions, assessing the annual trend might not be appropriate due to the fluctuation and instability of gastric cancer mortality in small areas. Trending analyses were thus performed for the overall country and 17 metropolitan cities and provinces only. In this model, a series of joined straight lines were fitted on the annual age-standardized mortality rates. The maximum number of joinpoints was identified based on the number of data points following the algorithmic recommendations of the Joinpoint Regression Program (ver. 4.3.0, Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) [22,23]. Accordingly, a maximum of 3 joinpoints for each region (except 1 joinpoint for Sejong city) was set, together with the log transformation of the rates in the model. Then, the annual percent changes (APCs) were calculated for each segment, and the average APCs (AAPCs) were obtained for the whole research period. The AAPC for each region was compared with the AAPC for the whole country to examine differences in gastric cancer mortality reductions between each city and province with the whole country.

Next, national data on age-specific gastric cancer mortality at 5-year age ranges (from 20 to 89 years only) between 2000 and 2020 were reconstructed for the age-period-cohort analysis. We estimated the single or double effects of age, period, and cohort by applying a log-linear model and conducted age-period-cohort analysis by applying an intrinsic estimator (IE) method [8]. Model performance was evaluated using the Akaike information criterion (AIC). In an exploratory analysis, age-specific by period, age-specific by birth cohort, and period-specific by birth cohort data for gastric cancer mortality were plotted. Data visualizations were performed using the 'ggplot2' package in the R program ver. 3.6.0 (R Software, R Foundation for Statistical Computing, Vienna, Austria), and age-period-cohort analysis was conducted using the 'apc' package in STATA software ver. 14.0 (Stata Corp., College Station, TX).

Then, the geographical distribution of age-standardized gastric cancer mortality in approximately 250 municipal areas in 2000-2020 was visualized in ArcGIS software ver. 10.4. The cutoff values for categories were selected using the Jenks natural breaks classification method, which optimizes the arrangement of continuous values into different clusters [24,25]. While the joinpoint regression was able to show mortality reductions of each city and province in comparison with the total population, spatial analysis aimed to investigate geographical variations and identify spatial clusters with high or low gastric cancer mortality rates. Here, we first calculated the global Moran's I statistic to examine whether the age-standardized gastric cancer mortality rates in each municipal region were geographically correlated. Overall, the global Moran's I values range from –1 (clustering of dissimilar values) to +1 (clustering of similar values), and the global Moran's I value of 0 refers to no geographical autocorrelation. A positive Moran's I value indicates neighbor features toward clustering, whereas a negative Moran's I value indicates neighbor features toward dispersion. Then, the local equivalent of the global Moran's I (local Moran's I, local indicator of spatial autocorrelation [LISA]) was estimated to elucidate the spatial autocorrelation between districts and their neighboring districts and determine municipal regions with high and low mortality rates as well as spatial outliers [26]. Spatial analysis was performed using the spatial autocorrelation (Moran's I) and cluster and outlier analysis (Anselin Local Moran's I) tools. The analysis is also called as hot-spot analysis, and results are provided with clusters, outliers, and nonsignificant areas. In high-high and low-low clusters, there is similar positive or negative autocorrelation among areas. In high-low and low-high outliers, a high-rate district is surrounded by low-rate districts and vice versa. Using data of 250 municipal areas in the spatial analysis was therefore able to identify several clusters and outliers of gastric cancer mortality across the country.

Finally, as exploratory analysis, we fitted the joinpoint regression model to examine the trends of participation rates of gastric cancer screening for the whole country and 17 cities and provinces, with a maximum of 1 joinpoint for each region and the log transformation for rates. All analyses were performed for the total population and sex-specific subgroups.

Results

1. Trends of gastric cancer mortality

Over the research period, age-standardized gastric cancer mortality rates decreased from 29.0 per person in 2000 to 7.9 per person in 2020 (Table 1, Fig. 1). Joinpoint regression analysis identified three join points, with significant APCs of

Table 1. Joinpoint regression analysis for age-standardized mortality rates in Korea between 2000 and 2020

Group	Age-standardized mortality rate (per 100,000)		Trend 1		Trend 2		Trend 3		Trend 4		AAPC (95% CI) (%)
	2000	2020	Year	APC (%)	Year	APC (%)	Year	APC (%)	Year	APC (%)	
Both sexes	29.0	7.9	2000-2002	−2.26[a]	2002-2011	−6.30[a]	2011-2018	−7.57[a]	2018-2020	−5.59[a]	−6.28 (−6.57 to −5.99)
Men	45.8	11.6	2000-2002	−1.61	2002-2010	−6.47[a]	2010-2020	−7.75[a]	-	-	−6.64 (−6.91 to −6.37)
Women	17.6	5.1	2000-2003	−3.91[a]	2003-2015	−6.51[a]	2015-2018	−8.84[a]	2018-2020	−1.86	−6.03 (−6.68 to −5.37)

AAPC, average annual percentage change; APC, annual percentage change; CI, confidence interval. [a]Significant difference.

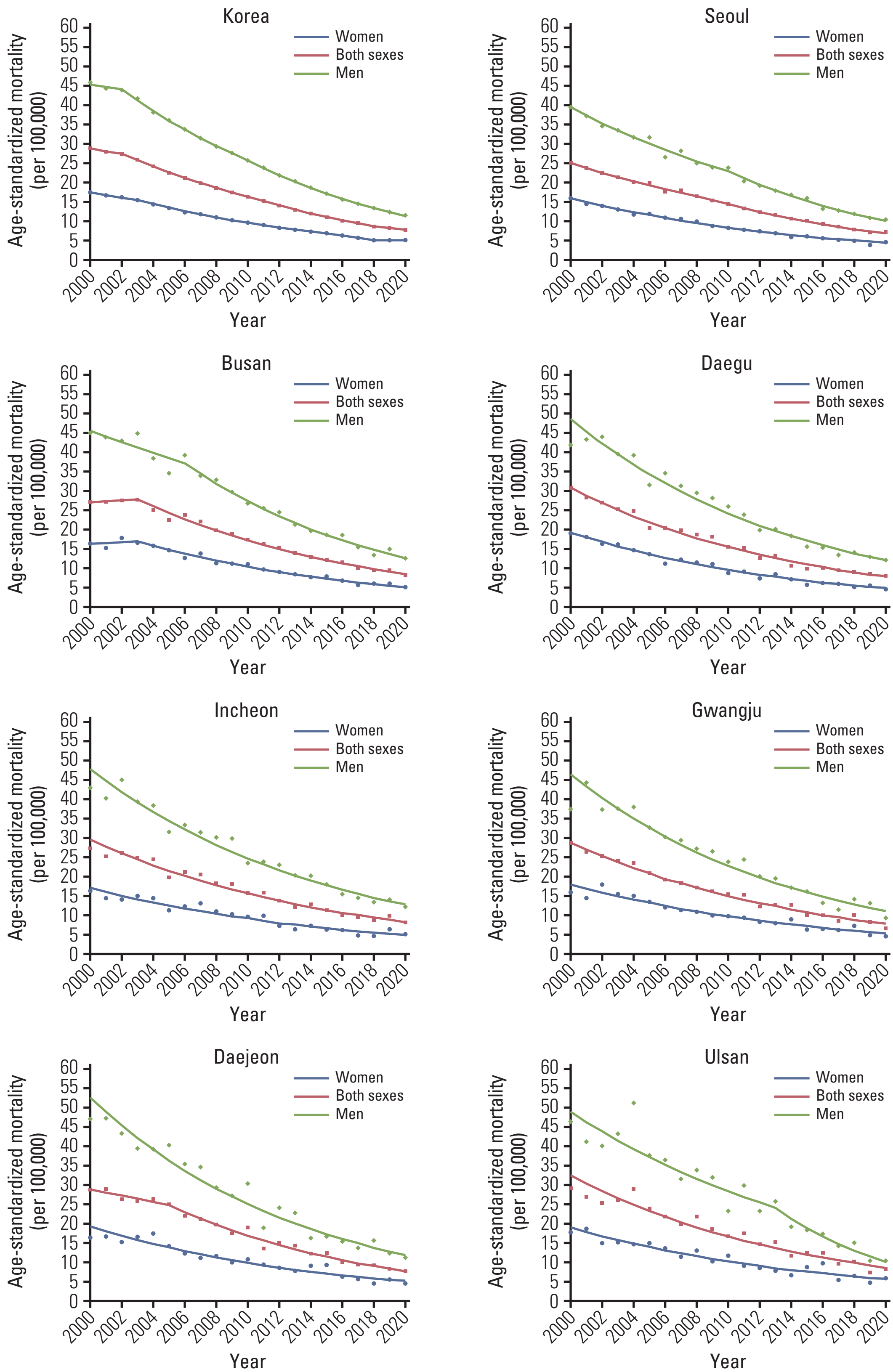
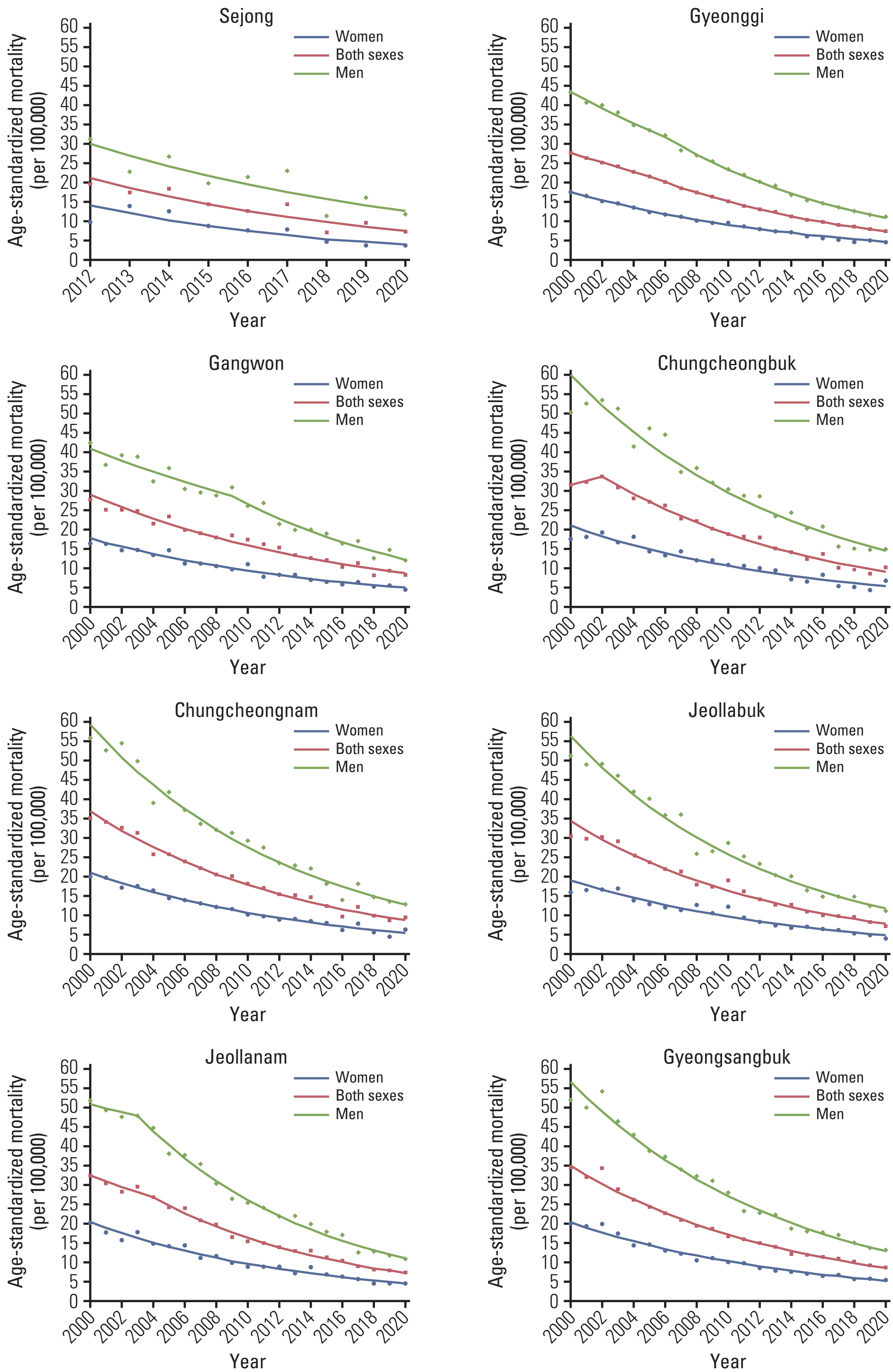


Fig. 1. Trends of age-standardized mortality rates in Korea between 2000 and 2020. *(Continued to the next page)*



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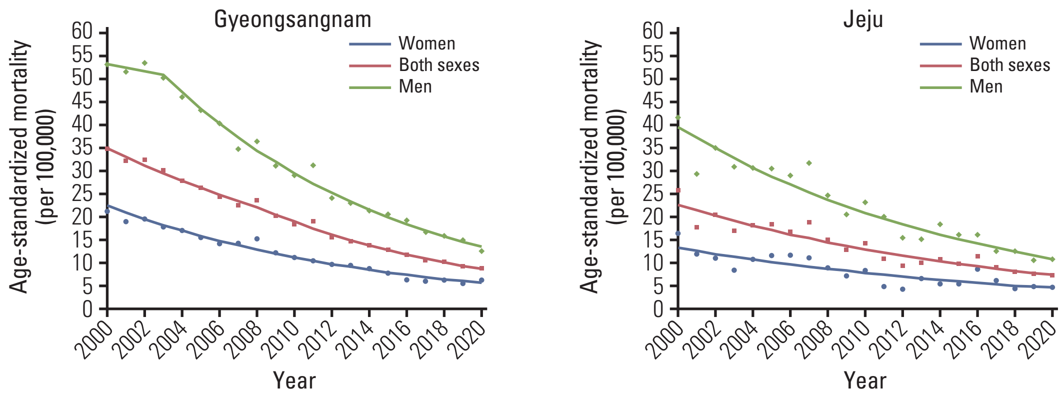

Fig. 1. *(Continued from the previous page)*

–2.26%, –6.30%, –7.57%, and –5.59% for the 2000-2002, 2002-2011, 2011-2018, and 2018-2020 periods, respectively. The AAPC (95% confidence interval [CI]) for gastric cancer mortality in the total population was –6.28% (–6.57% to –5.99%).

There were also downward trends of gastric cancer mortality in the sex-specific population, from 45.8 to 11.6 in men and from 17.6 to 5.1 in women per 100,000 persons (Table 1, Fig. 1). The reduction in age-standardized gastric cancer mortality did not differ between men and women, with AAPCs (95% CIs) of –6.64% (–6.91% to –6.37%) and –6.03% (–6.68% to –5.37%), respectively (p=0.091).

At the provincial level, gastric cancer mortality rates in 17 metropolitan cities and provinces also decreased from 2000 to 2020. Downward trends were observed for both sex-combined and sex-specific groups (Fig. 1, S1 Table).

2. Age-period-cohort analysis of gastric cancer mortality

Fig. 2 visualizes the effects of age, period, and birth cohort on gastric cancer mortality in both sexes combined and in men and women separately. Except for an increased rate in men aged 85-89 in the 2000-2004 period and those in the 1915-1919 birth cohort, there were declines in gastric cancer mortality for different age groups (Fig. 2A and B) across periods and birth cohorts. Within the same period, people who were in a more recent birth cohort exhibited lower rates of gastric cancer mortality among those who were born after 1920 (Fig. 2C).

The goodness of fit for the log-linear model and the IE age-period-cohort analysis for gastric cancer mortality is presented in Table 2. Considering the lowest AIC values, the age-cohort model showed a similar or better fit than the age-period-cohort effect using the IE. Furthermore, the estimates obtained from the age-period-cohort model are displayed in Fig. 3 and S2 Table. Gastric cancer mortality increased rapidly in both men and women within all age groups and decreased steadily across periods and birth cohorts. In contrast, women and both sexes combined who were born within 1960-1980 did not show a downward trend in the rate ratios of gastric cancer mortality.

3. Regional differences in gastric cancer mortality

Compared to the total population, there were greater reductions of gastric cancer mortality in Chungcheongnam-do (AAPC=–7.00%, p=0.01), Jeollabuk-do (AAPC=–7.10%, $p < 0.01$), Gyeongsangbuk-do (AAPC=–6.79%, p=0.01), whereas less reduction was observed in Jeju-do (AAPC=–5.35, p=0.02) (S1 Table). In men subgroup, there were greater reductions in Chungcheongnam-do, Jeollabuk-do, and Gyeongsangbuk-do, whereas greater reductions of gastric cancer mortality were observed in women living in Jeollanam-do ($p < 0.05$).

Fig. 4 shows the distribution of age-standardized gastric cancer mortality in 250 municipal regions of Korea in 2020. For the total population, the rates ranged between 1.4 and 18.0 per 100,000 and were classified into five categories (1.4 to 5.4, 5.4 to 7.4, 7.4 to 9.3, 9.3 to 12.0, and 12.0 to 18.0 per 100,000 persons). In the sex-specific analysis, these values fluctuated within wider ranges of 1.8 to 26.9 per 100,000 persons and 0 to 26.3 per 100,000 persons for men and women, respectively. In men, highest mortality rates were observed in Geochang-gun (26.9/100,000 persons in Gyeongsangnam-do), Haenam-gun (25.9/100,000 persons in Jeollanam-do), and Jeungpyeong-gun (24.5/100,000 persons in Chungcheongbuk-do). In women, highest mortality rates were observed in Yeongyang-gun (26.3/100,000 persons in Gyeongsangbuk-do), Bonghwa-gun (21.5/100,000 persons in Gyeongsangbuk-do), and Hampyeong-gun (19.5/100,000 persons in Jeollanam-do). The distribution of gastric cancer mortality rates in 2000, 2005, 2010 and 2015 is also presented in S3-S6 Figs. The districts in the highest categories in 2015

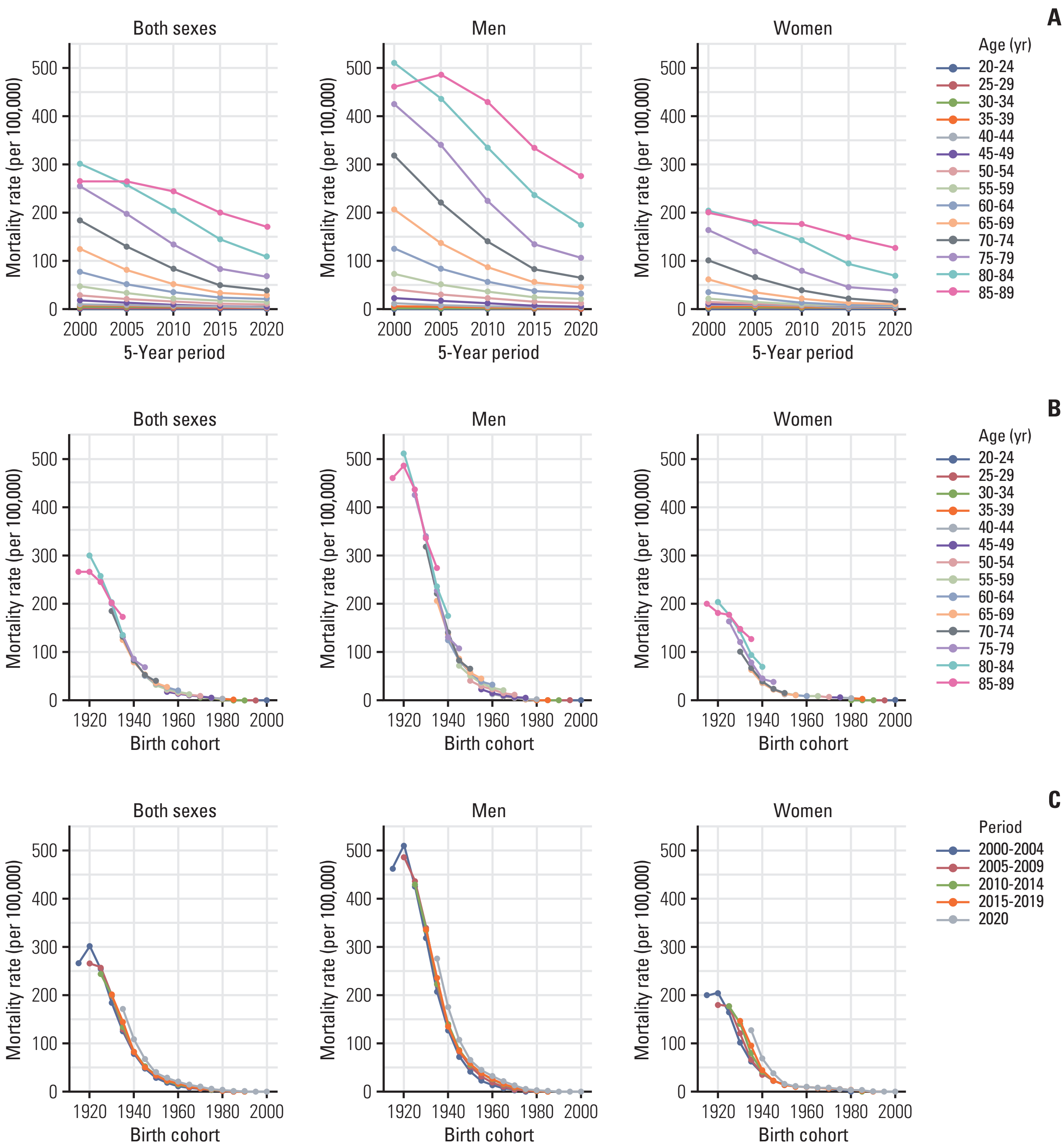

Fig. 2. Age, period, and birth cohort effects on gastric cancer mortality. (A) Age-specific gastric cancer mortality by period. (B) Age-specific gastric cancer mortality by birth cohort. (C) Period-specific gastric cancer mortality by birth cohort.

were more than those in 2020 for both total population and sex-specific groups.

To examine the spatial autocorrelation of gastric cancer mortality, S7 Fig. presents whether the districts close together exhibit similar rates. The likelihood that the clustered pattern could be the result of random chance was less than 1% for the total population (I=0.07, $p < 0.01$) and men (I=0.05, $p < 0.01$) but less than 10% for women (I=0.02, p=0.095). For

Table 2. Goodness of fit of the age-period-cohort model for gastric cancer mortality in Korea

Model	Both sexes			Men			Women		
	df	Log-likelihood	AIC	df	Log-likelihood	AIC	df	Log-likelihood	AIC
Age	42	–845.0	30.7	42	–1,560.0	56.2	42	–555.3	20.3
Period	52	–7,906.8	282.5	52	–16,011.6	572.0	52	–4,774.0	170.6
Cohort	39	–242.3	9.3	39	–480.8	17.8	39	–290.2	8.1
Age+period	39	–154.5	6.1	39	–185.5	7.2	39	–144.1	5.8
Age+cohort	26	–134.3	5.9[a)]	26	–143.6	6.2[a)]	26	–124.8	5.5[a)]
Period+cohort	48	–152.6	6.2	48	–196.2	7.7	48	–144.9	5.9
Age+period+cohort	24	–133.8	5.9[a)]	24	–140.9	6.2[a)]	24	–124.8	5.6

AIC, Akaike Information Criterion. [a)]Minimal AIC values.

better interpretation, Fig. 5 describes local spatial autocorrelation as five categories, including high-high and low-low clusters, high-low and low-high outliers, and nonsignificant areas. The list of municipal regions according to clusters and outliers is summarized in Table 3. Overall, we found clusters of high gastric cancer mortality in the central area for men (Chungcheongbuk-do, Jeollabuk-do, Gyeongsangbuk-do, and Gyeongsangnam-do) and the eastern area for women (Gyeongsangbuk-do). Clustering analysis of data in 2000, 2005, 2010 and 2015 also revealed higher rates of gastric cancer mortality in the Chungcheong-do and Gyeongsang-do areas than in other cities and provinces (S8-S11 Figs.).

4. Exploratory analysis for participation rates of gastric cancer screening

S12 Fig. shows the secular trend of participation rates of gastric cancer screening between 2010 and 2019. Overall, the screening rates for both sex-combined and sex-specific groups increased during the research period. This upward trend was also observed in all cities and provinces.

Discussion

In this study, we assessed the temporal trends, and effects of age, period, and birth cohort, and spatial patterns of gastric cancer mortality in Korea. We observed sustained declines for all of Korea and each province from 2000 (2012 for Sejong) to 2020. These trends were greatly driven by the birth cohort pattern, whereas the period contributed slightly to the decline in gastric cancer mortality in Korea. Additionally, our findings for the year 2020 showed clusters with high rates of gastric cancer mortality in the central area for men (Chungcheongbuk-do, Jeollabuk-do, Gyeongsangbuk-do, and Gyeongsangnam-do) and in the eastern area for women (Gyeongsangbuk-do).

In line with a previous study, we observed the peak of gastric cancer mortality for those who were born in 1920 and the decreasing rates across age groups in later birth cohorts [9]. This was caused through the introduction of healthier dietary changes in fruit, vegetable, and dairy food consumption in the Korean population since the 1980s [9]. Notably, women who were born between 1960 and 1980 did not experience a downward trend of gastric cancer mortality. A similar pattern was observed for the birth cohort from 1950-1970 in the study using data from 1983 to 2012, in which women in this cohort were also aged 40-60 years [10].

Helicobacter pylori infection has been well documented to increase the risk of atrophic gastritis, peptic ulcer, and gastric carcinoma by triggering the progression of precancerous lesions to atrophic gastritis and intestinal metaplasia [27]. In Korea, the estimated population attributable fractions of *H. pylori* to gastric cancer mortality were 75% for both men and women [28,29]. In accordance with the birth cohort effect on gastric cancer mortality in the present study, a downward trend of *H. pylori* seroprevalence attributable to the birth cohort effect was also observed [29]. In particular, data from approximately 20,000 health checkups in Korea in 2011 reported a lower *H. pylori* seroprevalence in the younger birth cohort than in the older birth cohort among individuals in the same age group [30].

The effect of calendar periods on the decrease in gastric cancer mortality can be explained by the uptake of screening programs, which can exhibit intermediate effects for gastric cancer mortality. Since 1999, the implementation of upper endoscopy or UGIS in the NCSP for gastric cancer has affected the clinical characteristics and management of gastric cancer [31]. The participant rates of endoscopy or UGIS increased from 7.4% in 2002 to 45.4% in 2011, with an APC % (95% CI) of 4.33 (4.02-4.63) [31]. In the present study, we continuously observed the upward trend of gastric cancer screening rates from 2010 to 2019 for all of Korea and some cities and provinces. Considering the effect screening methods, data from nearly 17 million Koreans in the NCSP

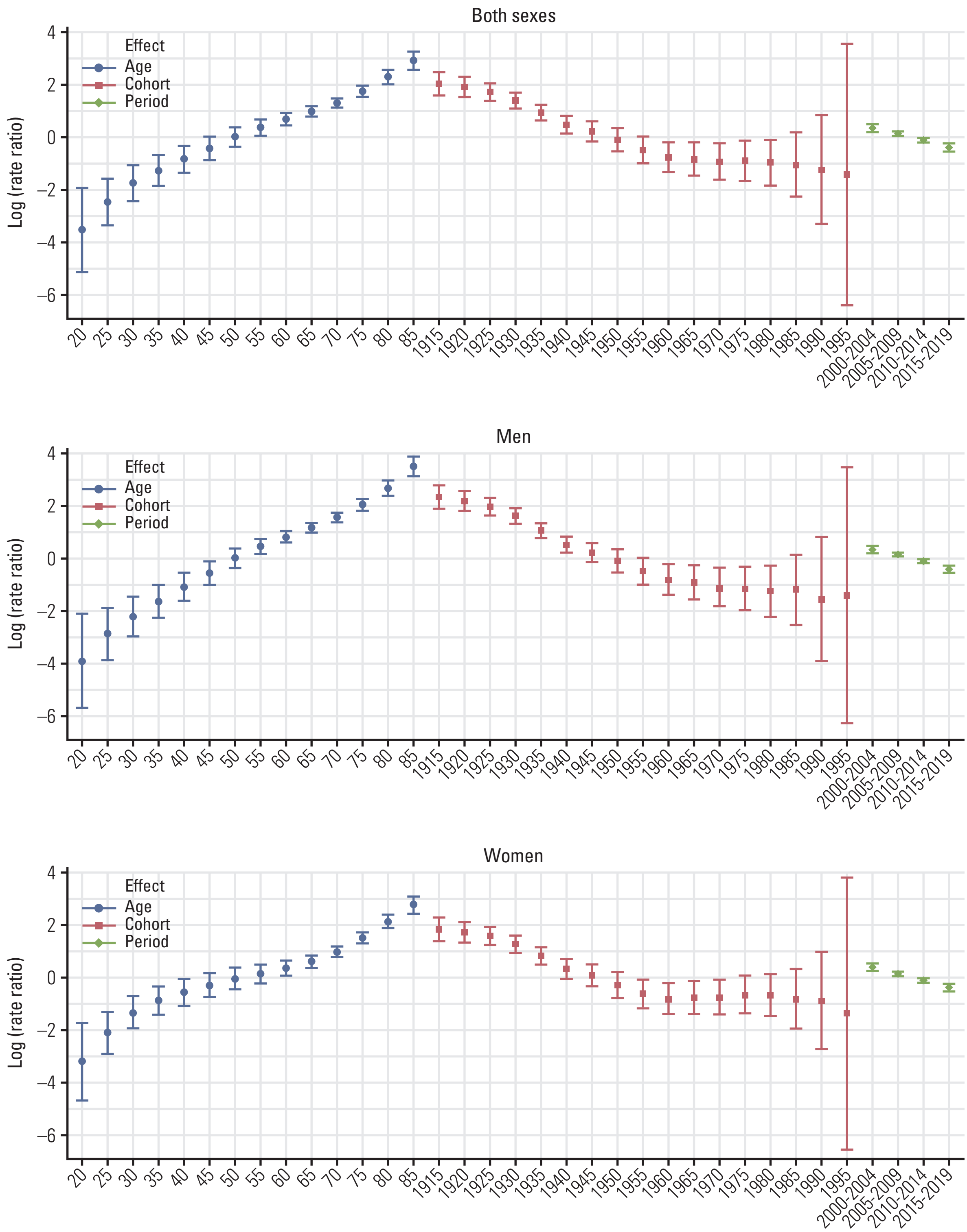

Fig. 3. Model estimates for age-period-cohort effects on gastric cancer mortality.

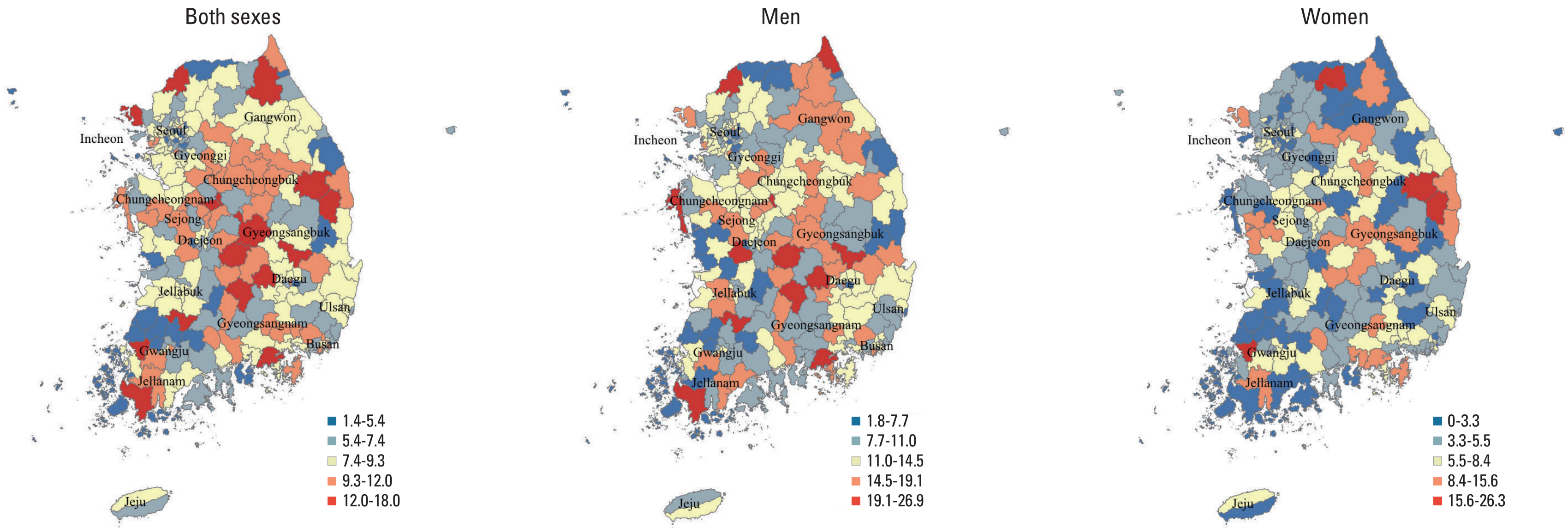

Fig. 4. Geographical distribution of age-standardized gastric cancer mortality rates (per 100,000 persons) in Korea, 2020.

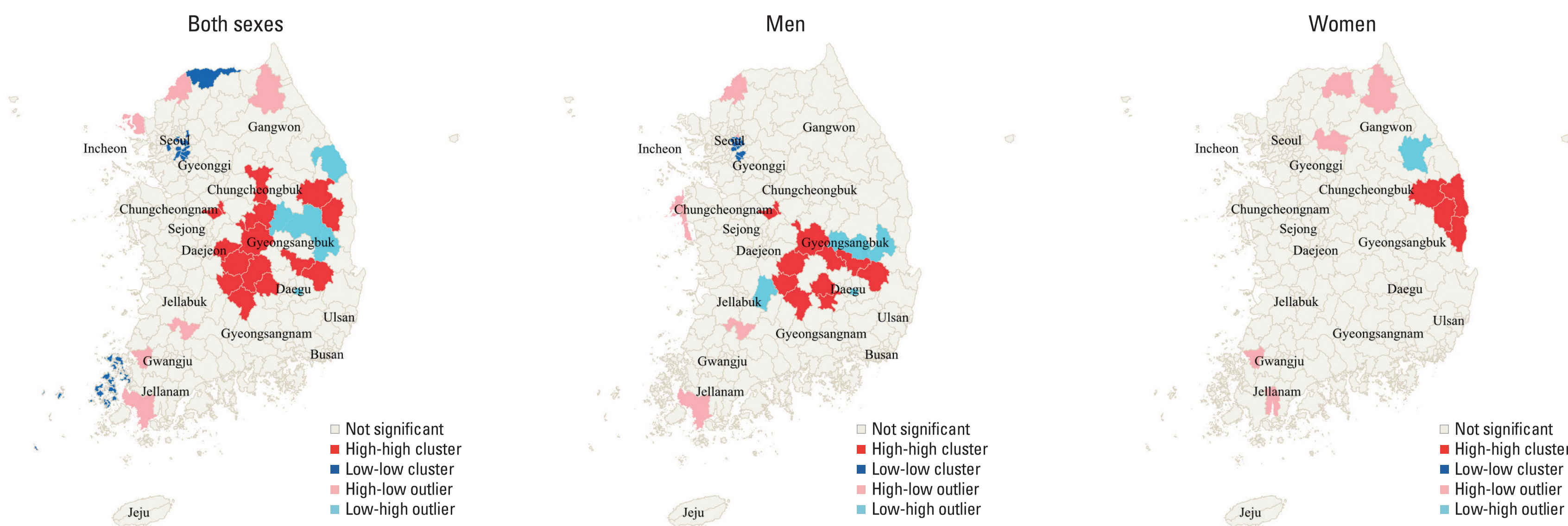

Fig. 5. Local Moran's I cluster maps for the spatial association of age-standardized gastric cancer mortality rates in Korea, 2020.

Table 3. List of regions in spatial clusters and outliers for gastric cancer mortality in Korea, 2020

Group	Cluster/ Outlier	Province	District (age-standardized gastric cancer mortality, per 100,000 persons)
Both sexes	High-high	Chungcheongbuk-do	Chungju-si (9.7), Boeun-gun (6.3), Yeongdong-gun (14.0), Jeungpyeong-gun (12.5), Jincheon-gun (7.2)
		Jeollabuk-do	Jangsu-gun (5.3)
		Gyeongsangbuk-do	Andong-si (5.8), Sangju-si (13.1), Mungyeong-si (11.7), Gyeongsan-si (6.9), Euiseong-gun (8.2), Yeongdeok-gun (7.8), Chilgok-gun (9.3), Uljin-gun (9.6)
	High-low	Incheon	Yongjin-gun (5.2)
		Gyeonggi-do	Gapyeong-gun (8.2)
		Gangwon-do	Goseong-gun (11.4)
		Jeollabuk-do	Gochang-gun (5.3)
		Jeollanam-do	Yeongam-gun (9.7), Yeonggwang-gun (3.5)
	Low-high	Daegu	Dalseo-gu (6.7)
		Gangwon-do	Hongcheon-gun (8.5)
		Gyeongsangbuk-do	Gumi-si (9.3), Yeongyang-gun (17.1), Bonghwa-gun (18.0)
	Low-low	Seoul	Yongsan-gu (5.3), Seongdong-gu (6.2), Songpa-gu (5.7), Gangdong-gu (7.9)
		Gyeonggi-do	Jungwon-gu (6.8), Euijeongbu-si (8.1), Pyeongteak-si (8.6), Guri-si (4.1), Namyangju-si (8), Hanam-si (8.2), Paju-si (9)
		Gangwon-do	Hwacheon-gun (7.8)
		Jeollabuk-do	Wansan-gu (7.6)
Men	High-high	Chungcheongbuk-do	Chungju-si (12.2), Jeungpyeong-gun (24.5), Jincheon-gun (13.2)
		Jeollabuk-do	Jangsu-gun (10.8)
		Gyeongsangbuk-do	Yeongju-si (13.9), Sangju-si (17.2), Mungyeong-si (16.3), Euiseong-gun (8.4), Seongju-gun (21.3), Chilgok-gun (15.0)
		Gyeongsangnam-do	Hapcheol-gun (8.8)
	High-low	Seoul	Jungrang-gu (13.7)
		Incheon	Yongjin-gun (6.2)
		Gyeonggi-do	Gapyeong-gun (12.7)
		Chungcheongbuk-do	Sangdang-gu (14.0)
		Jeollabuk-do	Gochang-gun (8.9)
		Jeollanam-do	Yeongam-gun (6.3)
	Low-high	Daegu	Dalseo-gu (9.7)
		Jeollabuk-do	Muju-gun (16.0)
		Gyeongsangbuk-do	Cheongsong-gun (5.0), Yeongyang-gun (13.5)
	Low-low	Gyeonggi-do	Euijeongbu-si (12.6), Guri-si (6.3), Paju-si (13.5)
		Seoul	Yongsan-gu (5.0), Seongdong-gu (6.9), Gwangjin-gu (6.2), Dongdaemun-gu (16.9), Gangnam-gu (7.5), Songpa-gu (7.2), Gangdong-gu (12.9)
Women	High-high	Gyeongsangbuk-do	Yeongdeok-gun (9.7), Cheongdo-gun (4.1), Uljin-gun (11.4), Ulleunggun (3.0)
	High-low	Gangwon-do	Yanggu-gun (0), Goseong-gun (1.5)
		Jeollanam-do	Haenam-gun (3.3), Yeonggwang-gun (1.8)
		Gyeongsangnam-do	Euichang-gu (7.3)
	Low-high	Gangwon-do	Cheolwon-gun (1.8)

revealed an approximately 50% decreased odds of gastric cancer mortality among those who performed upper endoscopy, with odds ratios (ORs) (95% CIs) of 0.53 (0.51, 0.56), 0.52 (0.50, 0.55), and 0.48 (0.42, 0.53) for the total population and men and women, respectively [6]. In contrast, UGIS exhibited a borderline effect on gastric cancer mortality reductions only [6]. This may therefore suggest that upper endoscopy uptake, but not UGIS, was attributable to the downward trend in gastric cancer mortality. Although the gastric cancer screening rates regardless of methods were higher for women than for men, the participant rates of upper endoscopy were higher for men than for women, and we thereby observed a greater AAPC in men than in women [31,32]. Furthermore, gastric cancer patients who experienced screening had lower odds of mortality than those without screening in both mild (patients treated with chemotherapy) and advanced (patients treated with gastrectomy and/or endoscopic procedure) stages [33].

In addition to early detection through screening, advances in gastric cancer treatments may contribute to the improvement of gastric cancer survival [34-36]. Despite the increase in clarithromycin resistance rates of *H. pylori* (9% in 1995, 13.8% in 2003, 16.7% in 2005, and 17.8% in 2018) [37-41], the eradication treatment rate rose significantly from 13.9% in 2005 and 19.3% in 2011 to 23.5% in 2017 [42]. Taken together, the seropositivity of *H. pylori* steadily decreased, with prevalence rates of 66.9%, 59.6%, 54.4%, and 51.0% in 1998, 2005, 2011, and 2015, respectively [43]. Additionally, *H. pylori* eradication treatments were reported to be associated with an approximately 2- to 5-fold higher possibility of hyperplastic polyp disappearance [44,45]. Data from the Korea National Health Insurance Service revealed that gastric cancer patients who underwent endoscopic resection or partial gastrectomy and medication for *H. pylori* within 1 year exerted a 21% to 61% reduced risk of metachronous lesion development compared to those who were administered medication more than 1 year after resection [46].

Since the 2000s, radical gastrectomy with D2 lymph node dissection has been considered a standard operation for gastric cancer [47]. Alternative methods have been introduced for the treatment of gastric cancer, such as laparoscopic surgery, function-preserving surgery, and endoscopic resection [47,48]. However, neither laparoscopy nor endoscopy showed any significant improvements in overall survival compared with gastrectomy [49,50]. In contrast, findings from multicenter randomized controlled trials showed the survival improvement effect of adjuvant chemotherapy in patients with completely resected gastric adenocarcinoma [51,52]. Nevertheless, the effect of these therapies on gastric cancer mortality in Korea requires further investigation.

The number of gastric cancer patients in cancer centers in metropolitan cities are higher than that in provinces (S13 Table) [53]. With the implementation of the expansion policy in 2013, cancer patients who previously limited their choices due to high medical costs were freer to select high-quality institutions that they preferred for care receiving [54]. Areas with high rates of gastric cancer mortality such as Chungcheong-do and Gyeongsang-do might thus show greater reductions compared to the overall reduction of the country. In other words, the disparity in gastric cancer mortality among cities and provinces tends to decrease during the period.

In terms of spatial patterns, data from the Korean National Cancer Incidence Database for regional variations of major cancer incidence in Korea at the municipal level between 1999 and 2013 revealed the highest age-standardized incidence of gastric cancer in Chungcheongbuk-do among men and in Gyeongsangbuk-do among women [55]. This is in line with our findings of high-high clusters of gastric cancer mortality in the Chungcheongbuk-do and Gyeongsangbuk-do areas. However, there is doubt about whether the high incidence reflects high mortality. By further obtaining municipal data on age-standardized incidence of gastric cancer in 250 districts, we explored the Pearson correlation between incidence rates in the 1999-2003, 2004-2008, and 2009-2013 periods with annual mortality rates during 2003-2020, 2008-2020, and 2013-2020, respectively. The strength of the correlation appeared to be weak to moderate only, with correlation coefficients between 0.12 and 0.67 (S14 Table).

Additionally, the peak of *H. pylori* seropositivity was found in individuals aged 50-59 years for the country overall and the Gyeonggi-do, Chungcheong-do, and Gyeongsang-do areas. This peak was observed in the younger group aged 40-49 years for Seoul and the older group aged 60-69 years for Gangwon-do, Jeolla-do, and Jeju [43]. Taken together, compared to Seoul, the *H. pylori* prevalence was higher in Chungcheong-do (OR, 1.33; 95% CI, 1.03 to 1.72), Gyeongsang-do (OR, 1.46; 95% CI, 1.20 to 1.77), and Jeolla-do (OR, 1.52; 95% CI, 1.19 to 1.94) after adjusting for multiple factors [43].

It is worth pointing out that this study investigated the temporal and spatial differences in gastric cancer mortality trends during a long and recent period in Korea. We retrieved age-standardized rates from a nationally representative database that covers the residential data of the whole population. Findings on national disparities in gastric cancer mortality may suggest priorities for effective prevention and treatment strategies to reduce regional inequalities in Korea. However, changes in administrative areas at municipal levels over the study period may lead to misclassification.

In conclusion, our study showed a downward trend in gastric cancer mortality among Korean men and women between 2000 and 2020 using national and regional data. This trend was much more attributed to birth cohort than calendar period effects. Regarding geographical area, we found high mortality due to gastric cancer in the Chungcheong-do and Gyeongsangbuk-do areas.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors. The study protocol was approved by the Institutional Review Board of Seoul National University (No. 2201-007-1286).

Author Contributions

Conceived and designed the analysis: Hoang T, Shin A.
Collected the data: Hoang T, Shin A.
Performed the analysis: Hoang T, Shin A.
Wrote the paper: Hoang T, Shin A.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
2. Wong MCS, Huang J, Chan PS, Choi P, Lao XQ, Chan SM, et al. Global incidence and mortality of gastric cancer, 1980-2018. JAMA Netw Open. 2021;4:e2118457.
3. G. B. D. Stomach Cancer Collaborators. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol. 2020;5:42-54.
4. Kim JH, Han KD, Lee JK, Kim HS, Cha JM, Park S, et al. Association between the National Cancer Screening Programme (NSCP) for gastric cancer and oesophageal cancer mortality. Br J Cancer. 2020;123:480-6.
5. Ministry of Health and Welfare Korea. National cancer screening guideline 2018. Sejong: Ministry of Health and Welfare; 2018.
6. Jun JK, Choi KS, Lee HY, Suh M, Park B, Song SH, et al. Effectiveness of the Korean National Cancer Screening Program in reducing gastric cancer mortality. Gastroenterology. 2017;152:1319-28.
7. Hong S, Won YJ, Lee JJ, Jung KW, Kong HJ, Im JS, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2018. Cancer Res Treat. 2021;53:301-15.
8. Heo J, Jeon SY, Oh CM, Hwang J, Oh J, Cho Y. The unrealized potential: cohort effects and age-period-cohort analysis. Epidemiol Health. 2017;39:e2017056.
9. Choi Y, Gwack J, Kim Y, Bae J, Jun JK, Ko KP, et al. Long term trends and the future gastric cancer mortality in Korea: 1983-2013. Cancer Res Treat. 2006;38:7-12.
10. Song M, Kang D, Yang JJ, Choi JY, Sung H, Lee Y, et al. Age and sex interactions in gastric cancer incidence and mortality trends in Korea. Gastric Cancer. 2015;18:580-9.
11. Rana N, Gosain R, Lemini R, Wang C, Gabriel E, Mohammed T, et al. Socio-demographic disparities in gastric adenocarcinoma: a population-based study. Cancers (Basel). 2020;12:157.
12. Li X, Deng Y, Tang W, Sun Q, Chen Y, Yang C, et al. Urban-rural disparity in cancer incidence, mortality, and survivals in Shanghai, China, during 2002 and 2015. Front Oncol. 2018;8:579.
13. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, Stubbs RW, Bertozzi-Villa A, Morozoff C, et al. Trends and patterns of disparities in cancer mortality among US counties, 1980-2014. JAMA. 2017;317:388-406.
14. Ruiz EF, Torres-Roman JS, Servan SA, Martinez-Herrera JF, Arce-Huamani MA, Carioli G, et al. Trends and geographic pattern of stomach cancer mortality in Peru. Cancer Epidemiol. 2019;58:193-8.
15. Ma C, Congly SE, Chyou DE, Ross-Driscoll K, Forbes N, Tsang ES, et al. Factors associated with geographic disparities in gastrointestinal cancer mortality in the United States. Gastroenterology. 2022;163:437-48.
16. Lee J, Sa J. Regional disparities in healthy eating and nutritional status in South Korea: Korea National Health and Nutrition Examination Survey 2017. Nutr Res Pract. 2020;14:679-90.
17. Ha K, Song Y, Kim HK. Regional disparities in the associations of cardiometabolic risk factors and healthy dietary factors in Korean adults. Nutr Res Pract. 2020;14:519-31.
18. Oh WS, Yoon S, Noh J, Sohn J, Kim C, Heo J. Geographical variations and influential factors in prevalence of cardiometabolic diseases in South Korea. PLoS One. 2018;13:e0205005.
19. Kim B. Regional disparity in adult obesity prevalence, and its determinants. J Health Info Stat. 2021;46:410-9.
20. Kang JH, Jung CY, Park KS, Huh JS, Oh SY, Kwon JH. Community care for cancer patients in rural areas: an integrated regional cancer center and public health center partnership model. J Hosp Palliat Care. 2021;24:226-34.
21. Korean Statistical Information Service [Internet]. Daejeon: Statistics Korea; 2022 [cited 2022 Sep 6]. Available from: https://kosis.kr/index/index.do.
22. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000;19:335-51.
23. National Cancer Institute. Joinpoint trend analysis software: number of joinpoints [Internet]. Bethesda, MD: National Cancer Institute; 2022 [cited 2022 Sep 6]. Available from: https://surveillance.cancer.gov/help/joinpoint/setting-parameters/method-and-parameters-tab/number-of-joinpoints.

24. Esri. ArcGIS program: data classification methods [Internet]. Seoul: Esri; 2022 [cited 2022 Sep 6]. Available from: https://pro.arcgis.com/en/pro-app/latest/help/mapping/layer-properties/data-classification-methods.htm.
25. Jenks GF. The data model concept in statistical mapping, 1967. In: Frenzel K, editors. International yearbook of cartography. Vol. 7. C. Gutersloh: Vertelsmans Verlag; 1967. p. 186-90.
26. Anselin L. Local Indicators of Spatial Association-LISA. Geogr Anal. 1995;27:93-115.
27. Diaz P, Valenzuela Valderrama M, Bravo J, Quest AFG. Helicobacter pylori and gastric cancer: adaptive cellular mechanisms involved in disease progression. Front Microbiol. 2018;9:5.
28. Shin A, Park S, Shin HR, Park EH, Park SK, Oh JK, et al. Population attributable fraction of infection-related cancers in Korea. Ann Oncol. 2011;22:1435-42.
29. Ko KP, Shin A, Cho S, Park SK, Yoo KY. Environmental contributions to gastrointestinal and liver cancer in the Asia-Pacific region. J Gastroenterol Hepatol. 2018;33:111-20.
30. Lim SH, Kwon JW, Kim N, Kim GH, Kang JM, Park MJ, et al. Prevalence and risk factors of Helicobacter pylori infection in Korea: nationwide multicenter study over 13 years. BMC Gastroenterol. 2013;13:104.
31. Lee S, Jun JK, Suh M, Park B, Noh DK, Jung KW, et al. Gastric cancer screening uptake trends in Korea: results for the National Cancer Screening Program from 2002 to 2011: a prospective cross-sectional study. Medicine (Baltimore). 2015;94:e533.
32. Ryu JE, Choi E, Lee K, Jun JK, Suh M, Jung KW, et al. Trends in the performance of the Korean National Cancer Screening Program for gastric cancer from 2007 to 2016. Cancer Res Treat. 2022;54:842-9.
33. Suh YS, Lee J, Woo H, Shin D, Kong SH, Lee HJ, et al. National cancer screening program for gastric cancer in Korea: Nationwide treatment benefit and cost. Cancer. 2020;126:1929-39.
34. Chen ZD, Zhang PF, Xi HQ, Wei B, Chen L, Tang Y. Recent advances in the diagnosis, staging, treatment, and prognosis of advanced gastric cancer: a literature review. Front Med (Lausanne). 2021;8:744839.
35. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci. 2020;21:4012.
36. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, Polkowski WP. Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer Manag Res. 2018;10:239-48.
37. Jung HK, Kang SJ, Lee YC, Yang HJ, Park SY, Shin CM, et al. Evidence-based guidelines for the treatment of Helicobacter pylori infection in Korea 2020. Gut Liver. 2021;15:168-95.
38. Lee JH, Ahn JY, Choi KD, Jung HY, Kim JM, Baik GH, et al. Nationwide antibiotic resistance mapping of Helicobacter pylori in Korea: a prospective multicenter study. Helicobacter. 2019;24:e12592.
39. Lee JW, Kim N, Kim JM, Nam RH, Chang H, Kim JY, et al. Prevalence of primary and secondary antimicrobial resistance of Helicobacter pylori in Korea from 2003 through 2012. Helicobacter. 2013;18:206-14.
40. Hwang TJ, Kim N, Kim HB, Lee BH, Nam RH, Park JH, et al. Change in antibiotic resistance of Helicobacter pylori strains and the effect of A2143G point mutation of 23S rRNA on the eradication of H. pylori in a single center of Korea. J Clin Gastroenterol. 2010;44:536-43.
41. Kim JM, Kim JS, Jung HC, Kim N, Kim YJ, Song IS. Distribution of antibiotic MICs for Helicobacter pylori strains over a 16-year period in patients from Seoul, South Korea. Antimicrob Agents Chemother. 2004;48:4843-7.
42. Lim SH, Kim N, Kwon JW, Kim SE, Baik GH, Lee JY, et al. Trends in the seroprevalence of Helicobacter pylori infection and its putative eradication rate over 18 years in Korea: a cross-sectional nationwide multicenter study. PLoS One. 2018;13:e0204762.
43. Lee JH, Choi KD, Jung HY, Baik GH, Park JK, Kim SS, et al. Seroprevalence of Helicobacter pylori in Korea: a multicenter, nationwide study conducted in 2015 and 2016. Helicobacter. 2018;23:e12463.
44. Nam SY, Park BJ, Ryu KH, Nam JH. Effect of Helicobacter pylori eradication on the regression of gastric polyps in National Cancer Screening Program. Korean J Intern Med. 2018;33:506-11.
45. Nam SY, Park BJ, Ryu KH, Nam JH. Effect of Helicobacter pylori infection and its eradication on the fate of gastric polyps. Eur J Gastroenterol Hepatol. 2016;28:449-54.
46. Kim HJ, Kim YJ, Seo SI, Shin WG, Park CH. Impact of the timing of Helicobacter pylori eradication on the risk of development of metachronous lesions after treatment of early gastric cancer: a population-based cohort study. Gastrointest Endosc. 2020;92:613-22.
47. Jeong O, Park YK. Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients. J Gastric Cancer. 2011;11:69-77.
48. Park CH, Yang DH, Kim JW, Kim JH, Kim JH, Min YW, et al. Clinical practice guideline for endoscopic resection of early gastrointestinal cancer. Clin Endosc. 2020;53:142-66.
49. Yu J, Huang C, Sun Y, Su X, Cao H, Hu J, et al. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. JAMA. 2019;321:1983-92.
50. Meng FS, Zhang ZH, Wang YM, Lu L, Zhu JZ, Ji F. Comparison of endoscopic resection and gastrectomy for the treatment of early gastric cancer: a meta-analysis. Surg Endosc. 2016;30:3673-83.
51. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379:315-21.
52. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810-20.
53. National Cancer Center. Clinical Oncology Network for uNifying Electronic mediCal daTa (CONNECT) [Internet]. Goy-

ang: National Cancer Center; 2022 [cited 2022 Spe 6]. Available from: https://cancerportal.kr/.
54. Cho S, Chang Y, Kim Y. Cancer patients' utilization of tertiary hospitals in Seoul before and after the benefit expansion policy. J Prev Med Public Health. 2019;52:41-50.
55. Won YJ, Jung KW, Oh CM, Park EH, Kong HJ, Lee DH, et al. Geographical variations and trends in major cancer incidences throughout Korea during 1999-2013. Cancer Res Treat. 2018;50:1281-93.