Statistical Data

Regional differences in colorectal cancer mortality between 2000 and 2013 in Republic of Korea

Short Title: Regional differences in colorectal cancer mortality in Korea

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ABSTRACT

Objective: Colorectal cancer (CRC) is the 4th common site for cancer death in Republic of Korea. The aim of this study was to describe the trends of colorectal cancer mortality by regions.

Methods: CRC mortality trends in Republic of Korea by region were described using a Joinpoint regression model in both sexes. The annual percent changes (APC) were calculated for each segment. Visualization of the changes in mortality rate of colorectal cancer death rates by 16 geographic areas in both sexes between 2000-2004 and 2009-2013 were also conducted.

Results: CRC mortality rates of men showed decreasing trend after increase in Daegu, Gyeongsangnam-do and Chungcheongbuk-do between 2000 and 2013 based on the joinpoint model. While, Gwangju, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do showed increase in CRC mortality during the same period. For women, CRC mortality of Seoul, Incheon, Daejeon and Gyeongsangnam-do started to decrease in 2005, 2003, 2007 and 2006 respectively. The mortality rate for CRC in the eastern regions, which had relatively low rates of CRC among men in 2000 to 2004, reached a level similar to that in the northwestern regions of 2009 to 2013, while the highest CRC mortality rates in women was observed in Chungcheongbuk-do.

Conclusions: Reduction in CRC mortality varied across 16 metropolitan cities and provinces in men, and the visualization pattern showed that the east side of South Korea had the least progress in mortality reduction.

Key words: Colorectal cancer (CRC); Mortality; Geographic Difference; Health geographical disparities
INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death in both sexes in worldwide 1-3 and the 4th cause of cancer death in Republic of Korea with crude rate of 18.5/100,000 for men and 13.8/100,000 for women in 2012 4. Mortality of CRC have been decreasing in countries in Europe, Oceania, as well as in Asia for the past several decades 5-7. This decrease may be affected by increased uptake of CRC screening 6,8,9 or differences in socioeconomic status.10-12

In previous studies, it has been projected that CRC mortality could be reduced with appropriate interventions 13,14, and deliberate public health action is being implemented in selected regions to accomplish the goal 15-18. Besides, disparities by geographical regions contributes in variation of CRC mortality 9,11,19. The geospatial approach describing the trends of CRC mortality would be highly useful to better understand the factors which contribute to the overall CRC outcomes differed by regions.5,20

In the Republic of Korea, decrease in CRC mortality was observed among women since year 2004, whereas mortality of men was stabilized since 2002 2. However, the extent to which these decrease varies across sex and its influence on the regional characteristics of Korean CRC death rates are not documented in previous studies. Although the wide geographical variation in the mortality of CRC is evident, there was lack of evidence which shows regional differences considered with age and sex.

To this end, the present study aimed to explore the potential differences in trend of CRC mortality by geographical areas and both sexes in the Republic of Korea.
Therefore, we first analyzed CRC mortality trends in Republic of Korea from 2000 through 2013 by provinces and sex, then the change in geographic visualization patterns of rates for 2 time intervals, 2000–2004 and 2009–2013 were also examined.

Methods

Materials

Age-specific mortality rate for CRC data from 2000 through 2013 for the 16 metropolitan cities and provinces (1 Special city, 6 metropolitan cities, 8 provinces, and Jeju Special Self-Governing Province) were obtained from the Korean Statistics Information Service (KOSIS) database as reported below the section of “Cause of Death” statistical database. Mortality for cancer of the colon, rectum and anus (ICD-10 code C18-C21) were extracted using computer network (KOSIS, e-Nara Indicator) and standardized by using the mid-year population of the year 2005 of the Republic of Korea and expressed per 100,000 populations.21,22

CRC mortality and trends

CRC mortality trends in Republic of Korea by region were described using a Joinpoint regression model to determine at which year the linear trend changed significantly in each of men and women. The Joinpoint regression models were fitted with a series of joined straight lines on a log scale to the annual age-standardized rates (ASRs). For each model, we allowed a maximum of 2 join-points for each area. The annual percent changes (APC), which are the slopes of the change in death rates
were calculated for each segment. For each region, we also calculated the change in death rates between the 2000-2004 and 2009-2013 using rate ratio (2000-2004 to 2009-2013), with 95% confidential interval in both sexes. All statistical tests were 2 sided (p<0.05). Joinpoint Regression Program version 4.2.0.1 were used to statistical analysis (https://surveillance.cancer.gov/joinpoint/download).

**Geographic patterns of CRC death rates**

To visualize the changes in mortality rate by geographic patterns of CRC death rates in both sexes between 2000-2004 and 2009-2013, we used regional maps using Korea ‘map shp’ from Statistical Geographic Information Service with R version 3.1.0 (http://cran.r-project.org) package of Rgdal (R for Geospatial Data Abstraction Library: https://r-forge.r-project.org/projects/rgdal/). Source map were driven by Republic of Korea shp (Shape file) from SGIS. For each time interval, age-standardized rates for each state were sorted in descending order of rates and grouped into 8 categories. The highest and lowest categories are approximately the 10th and 90th percentiles, whereas the remaining regions were divided into 6 equivalent groups. The color gradient in the maps reflect the CRC burden, with regions with the highest CRC mortality rate assigned the darkest color.

**RESULTS**

Although the CRC mortality has been stabilized in men since 2003 nationwide, the mortality kept increasing until 2013 in Gwangju, Jeollabuk-do, Jeollanam-do, and
Gyeongsangbuk-do with significant APCs. (Table 1 and Figure 1). Nationwide, the APCs in CRC death rates of women started to be decreased since 2004 (Table 2 and Figure 1). According to joinpoint regression among women, mortality decreased significantly in Seoul since 2005, Incheon since 2003, Daejeon since 2007 and Gyeongsangnam-do since 2006. Figure 2 illustrates the ASR of CRC mortality during 2000-2004 and 2009-2013 in both sexes by geographical regions. During 2000-2004 in men, the highest CRC mortality were observed in metropolitan areas such as Daejeon, Incheon and Seoul, the lowest mortality was observed in Gangwon-do, Jeollanam-do and Jeju-do. During 2009 to 2013, the highest mortality in men was found in Gwangju, and Inchoen. In specific for men, the west sides of South Korea showed higher mortality rate in 2000-2004, however, in 2009-2013 the mortality rate of CRC in the eastern regions increased, reaching a level similar to that in the western regions.

In contrast, death rates of all cities and provinces decreased or were stable in women. The mortality rate ratios between 2000-2004 and 2009-2013 were the lowest in Incheon (0.91) followed by Chungcheongbuk-do (0.93), whereas Jeju-do (1.11) and Gwangju (1.08) showed the highest rate ratios, although none of the rate ratios were statistically significant.

**DISCUSSION**

In this study, the data provided are the most recent regional information of CRC in South Korea from KOSIS. Mortality data of CRC in South Korea from 16 metropolitan cities and provinces are presented. Similar with other countries’
geographical studies\textsuperscript{5,23}, we analyzed temporal trends in age-standardized CRC death rates from 2000 through 2013 by geographical areas in both sexes and the change in geographic patterns of rates for 2 time intervals, 2000–2004 and 2009–2013. The study showed that more significant regional differences in CRC mortality were shown in men by even in the rural areas (Gangwon-do, Jeollabuk-do, Jeollanam-do, and Gyeongsangbuk-do) where mortality increased from 2000 to 2013. In Republic of Korea, cancer related burden is expected to show a rapid growth with the increasing cancer incidence and mortality.\textsuperscript{24-26}

We also found that the time trends of some provinces indicated that there were joinpoint around 2004. In Republic of Korea, the age-standardized mortality rate of men for CRC was increased from 1984 to 2003, then remained stable thereafter, while the CRC mortality rate in women started to be decreased since 2004.\textsuperscript{27} Those of findings have been affected by an underlying birth-cohort pattern. Among both sexes, while the period effects also steadily increased until 2004\textsuperscript{2}, the cohort effect curve showed decreasing patterns since the 1919, which investigated the decreasing relative risk of CRC mortality in recent younger cohorts.

In addition, in Korea, the national cancer screening program (NCPS) for CRC using fecal occult blood test (FOBT) began in 2004\textsuperscript{28}. People who are within the lower 50\% of insurance premium bucket of the National Health Insurance Corporation (NHIC) are the targeted population for the NCSP. Therefore, introduction of screening program may contribute to improved CRC survival and consequent reduction in mortality in Korea\textsuperscript{29}. In Korea, CRC incidence was rapidly increased until 2011, then started to be decreased in both men and women. Introduction of national
cancer screening program may affect the reduction of mortality rate and transient
ingcrease in incidence due to finding of prevalent cases during the initial period of
screening program.

To the best of our knowledge, this is the first study to report on the regional
differences in CRC mortality in Republic of Korea. In prior studies conducted in USA,
socio-economic status (SES) inequalities in CRC death by states\textsuperscript{11,20} were
investigated using SEER cancer statistic data.\textsuperscript{5} Earlier studies suggested that there
were significant geographic disparities in USA for overall CRC mortality trends, and
those of differences are explained by the inequality factor of education\textsuperscript{11,20} or uptake
of screening rates.\textsuperscript{5} In addition, in China, there was study investigating CRC mortality
calculated by area, sex and age category groups.\textsuperscript{23}

Considering with those of other studies, possible explanations for geographical
disparities in CRC death rates in Republic of Korea includes multiple factors such as
uptake of screening, several known behavioral\textsuperscript{30,31} and lifestyle factors such as
physical inactivity, unhealthy dietary habits.\textsuperscript{10-12,32} From the previous studies, regions
whose uptake of CRC screening was lower were more likely to have CRC cases with
advanced stages\textsuperscript{4,33} and were related with lower proportion of mortality decreasing
rates compared with other regions.\textsuperscript{5} In this study, we did not analyze primary causing
factors affecting CRC death rates according to the geographical patterns, leaving the
possibility that this disparity can be explained by multiple factors due to the
geographical differences.\textsuperscript{5,10} While among other lifestyle factors, obesity may increase
the risk of CRC\textsuperscript{34,35}. Based on the data of NHIS, the top ranking of obesity prevalence
in 2015 was observed in Jeju-do, Gangwon-do, Incheon, and Jeollado area, which
showed the increasing rates of CRC from 2000-2004 to 2009-2013 in men.

Even if data on regional variation in CRC treatment are limited, CRC survivors residing in rural areas or poorer provinces are less likely to receive appropriate and fast treatment than residing in urban or more affluent areas.\textsuperscript{10,36} From previous studies, people with lower SES may delay their treatment for CRC due to diverse factors, including lack of treatment related knowledge, care burden, and limited medical accessibility.\textsuperscript{10,37} CRC patients residing in rural areas or poorer neighborhoods are less likely to receive adjuvant chemotherapy than patients residing in urban or more affluent areas.

A limitation of our study is the validity of death certificates which can affect our results. The Cause of Death Statistics of Korea is primarily based on death certificates. In previous study, overall accuracy of the Cause of Death Statistics was 91.9\%.\textsuperscript{39} In addition, if there were no available death certificates, deaths were classified as unknown causes. Other previous studies identified that overall 18.3\% of deaths were classified as unknown causes and proportion of unknown causes was vary region to region\textsuperscript{40}. In other aspects, overall, as proportion of death certificates issued by physicians was steadily increased\textsuperscript{41}, proportion of unknown cause of death steadily decreased. This could contribute to little change in CRC mortality rate in most areas. However, since CRC is major neoplasm, its diagnosis is more likely to be fairly accurate.

The time of trends examined from 2000 through 2013 may also be limitation. Although cause-specific mortality data was available from 1983, therefore, we could calculated the yearly ASR per 100,000 based on the KOSIS from 1983 to 2013.
However, because we wanted to look at the recent trends in the past 10 years, we only selected the data from 2000 to 2013.

Therefore, in our study we chose the year of 2000 as the observation starting point. In addition, although we tried to explain the regional differences of CRC mortality with prevalence of known risk factors such as smoking, alcohol consumption and especially for screening, a further study to investigate the reasons for regional differences in trends of CRC mortality based on more descriptive evidence should be pursued.

Nevertheless, the main strength of this study is to examine representative CRC mortality trend in Korea by using nationwide data. Because Joinpoint regression usually needs a large sample size, although statistical power to detect a significant APC depends on a value size of APC and rate per population. In addition, this study first showed the geographical pattern of CRC death rates using visualization data. We found that the mortality rate for CRC in the eastern regions such as Deagu after 2006, Chongchengbuk-do after 2004, and Gyeongsangnam-do after 2004, which had relatively lower rates than that of the men in 2000 to 2004, reached a level similar to that in the northwestern regions of 2009 to 2013. Northwestern regions such as Incheon and Daejeon showed stable and higher CRC over the observation period in men, Gwangju, Jeollabuk-do, Jeollanum-do, and Gyeongsamgbuk-do which were placed in the southwest showed an increasing trend of CRC mortality. Generally, the regional disparity of CRC death rates decreased in men from 2000-2004 to 2009-2013.

In conclusion, regional variation in CRC mortality of men became less apparent between 2000-2013. Still, based on the APC analysis, CRC mortality has started to

Authors’ Contributions:
Study concept and design: Aesun Shin
Statistical Analysis: Hyeong Taek Woo, Jin Ah Sim
Spatial Analysis: Jong Hun Mo, Jin Ah Sim
Provision of study materials or patients: Statistic Korea, Republic of Korea
Collection and assembly of data: Jin Ah Sim, Hyeong Taek Woo
Data analysis and interpretation: Jin Ah Sim, Hyeong Taek Woo, Aesun Shin, Young Ho Yun
Manuscript writing: Jin Ah Sim, Hyeong Taek Woo, Aesun Shin, Young Ho Yun
Administrative, technical, or material support: Aesun Shin

Conflict of Interest Disclosures: The authors declare no conflicts of interest.

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8
<table>
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<tr>
<th>Provinces</th>
<th>(2010 Population size)</th>
<th>Age standardized mortality (2000-2013)</th>
<th>Mortality Rate(Male) 2000~2004</th>
<th>Rate ratios (95% CI) 2009~2013</th>
<th>Trend 1 Years</th>
<th>APC Years</th>
<th>Trend 2 Years</th>
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<td>16.05 17.94</td>
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<td>10.81* 2004-2013 -0.9</td>
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<td>4.36 2006-2013 -4.22*</td>
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<tr>
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<td>0.39 2003-2010</td>
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</table>

Mortality rate is per 100,000, age adjusted to the 2005 Republic of Korea standard population. RR, Rate Ratios; CI, Confidential Interval with IACR method; APC, Annual Percent Change.

* APC is significantly different from zero at alpha = 0.05
### Table 2. Colorectal cancer (CRC) mortality per 100,000 and trends in women 16 provinces, Republic of Korea, 2000-2013

<table>
<thead>
<tr>
<th>Provinces</th>
<th>Age standardized mortality rate (2000–2013)</th>
<th>Mortality Rate(Female)</th>
<th>Rate ratios (95% CI)</th>
<th>Trend 1</th>
<th>Trend 2</th>
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<td>8.78</td>
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<td>7.9 7.8 8.4 9.6 9.3 9.0</td>
<td>8.4 9.0 8.7</td>
<td>9.5</td>
<td>9.3</td>
<td>7.8</td>
</tr>
<tr>
<td>Jeollabuk-do (898,414)</td>
<td>7.0 6.3 8.0 9.9 8.7 8.6</td>
<td>10.1 8.8</td>
<td>8.5</td>
<td>9.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Jeollanam-do (882,797)</td>
<td>6.7 6.6 6.2</td>
<td>8.0 9.1 8.4</td>
<td>5.5 5.7</td>
<td>7.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Gyeongangbuk-do (1,200,880)</td>
<td>7.9 8.7 9.4</td>
<td>14.0 10.0</td>
<td>9.1 9.3</td>
<td>8.7</td>
<td>9.5</td>
</tr>
<tr>
<td>Gyeongsangnam-do (1,556,885)</td>
<td>7.4 8.0 7.8</td>
<td>7.5 9.0</td>
<td>9.5</td>
<td>9.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Jeju-do (266,890)</td>
<td>4.4 5.2 6.5</td>
<td>8.0 6.6</td>
<td>8.7</td>
<td>7.9</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Mortality rate is per 100,000, age adjusted to the 2005 Republic of Korea standard population. RR, Rate Ratios; CI, Confidential Interval with IACR method; APC, Annual Percent Change.

* APC is significantly different from zero at alpha = 0.05
Figure 1. Trends in colorectal cancer mortality for each selected province, 2000-2013
Figure 2. Colorectal cancer age-standardized mortality rates a by 16 provinces, 2000-2004 to 2009-2013

(A) Male mortality rate 2000-2004
(B) Male mortality rate 2009-2013
(C) Female mortality rate 2000-2004
(D) Female mortality rate 2009-2013


a. Age-standardized rates for each states and periods by sex were sorted in descending order and grouped into 8 categories (6.27-7.85, 7.85-9.43, 9.43-11.02, 11.02-12.61, 12.61-14.19, 14.19-15.77, 15.77-17.35, 17.35-18.94). Unit: /100,000