RESEARCH ARTICLE

Recent Decrease in Colorectal Cancer Mortality Rate is Affected by Birth Cohort in Korea

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Abstract

Background: Colorectal cancer mortality has started to decrease in several developed countries in Asia. The current study aimed to present the long-term trends in colorectal cancer mortality in Korea using joinpoint analysis and age-period-cohort modeling. Materials and Methods: The number of colorectal cancer deaths and the population for each 5-year age group were obtained from Statistics Korea for the period 1984-2013 for adults 30 years and older. Joinpoint regression analysis was conducted to determine changes in trends in age-standardized mortality rates, and age-period-cohort analysis was performed to describe trends in colorectal cancer mortality using the intrinsic estimator method. Results: In men, the age-standardized mortality rate for colorectal cancer increased from 1984 to 2003, and the mortality rates stabilized thereafter, whereas the mortality rate of colorectal cancer in women has decreased since 2004. The age-specific mortality rate of colorectal cancer increased in both men and women over time, whereas decreases in the age-specific mortality rate in younger cohorts were observed. In the age-period-cohort analysis, old age and recent period were associated with higher mortality for both men and women. The birth cohort born after 1919 showed reduced colorectal cancer mortality in both men and women. Conclusions: Our study showed a recent decreasing trend in colorectal cancer mortality in women and a stable trend in men after 2003-2004. These changes in colorectal cancer mortality may be attributed to birth cohort effects.

Keywords: Colorectal cancer - mortality - trends - birth cohort - Korea

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Introduction

Colorectal cancer (CRC) is the fourth most common cause of death from cancer in men (373,639 cases, 8.0% of the total) and the third in women (320,294 cases, 9.0% of the total) worldwide (Ferlay et al., 2013). According to the Korean National Cancer Center, the incidence of CRC, the third most common cancer in Korea, has increased from 21.2/100,000 people in 1999 to 39.0/100,000 people in 2011 (National Cancer Information Center, 2014). However, a decrease in CRC mortality has been observed in economically advanced regions, such as Japan, Hong Kong and Singapore (Shin et al., 2013). A reduction in CRC mortality has also been observed in most western and northern European countries (Bosetti et al., 2009) and the United States (Jemal et al., 2010).

Recent studies have shown the importance of considering all three effects simultaneously (age, period and cohort experiences) in studying health outcomes (Yang, 2008; Reither et al., 2014). Age-period-cohort (APC) modeling enables the separation of the effects of age, period, and cohort and the description of their simultaneous effects on disease trends. APC analysis provides clues for particular agents or risk factors for disease and mortality by depicting the entire complex of social and environmental factors that create these risk factors (Yang, 2008). Several studies have been conducted to examine birth cohort effects on CRC incidence and mortality rates in the USA (1994), Spain (2010), Norway (2002), the Netherlands (2009), Singapore (2008), Japan (2006), and Taiwan (2012) (Chu et al., 1994; Svensson et al., 2002; Minami et al., 2006; Kok et al., 2008; van Steenbergen et al., 2009; Abente et al., 2010; Su et al., 2012).

However, currently, no epidemiological study has analyzed the recent trends and temporal changes in CRC mortality in the Korean population. Therefore, the aim of this study was to examine secular trends in CRC mortality and distinguish the effects of age, time period, and birth cohort on the trends in CRC mortality rate from 1984 to 2013 in Korea.

Materials and Methods

Data sources

Data on the annual number of colorectal cancer deaths and corresponding population from 1984 to 2013 were obtained from the Statistics Korea (2015). As there were

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too few CRC deaths in people younger than 30 years, analyses were restricted to those older than 30 years (Bosetti et al., 2011). Mortality data for colorectal cancer were defined as C18-C21 from the 10th revision of the International Classification of Diseases (ICD-10) (Fritz et al., 2000).

To evaluate general CRC trends for each sex, the data were arranged in six 5-year periods (1984-1988 to 1999-2013), and eleven 5-year age groups (30-34 to 80+ years). These age groups and calendar periods involved fourteen overlapping 5-year cohorts because of the relation cohort=period-age. Segi's world standard population data were used as the standard population.

Statistical analysis

Age-standardized mortality rates (ASMRs) of colorectal cancer were calculated to conduct joinpoint regression analysis by multiplying the 5-year interval age-specific mortality rate by the weights of the corresponding age groups of Segi's world standard population. The ASMRs are expressed as rates per 100,000 person-years for the periods 1984-1988, 1989-1993, 1994-1998, 1999-2003, 2004-2008 and 2009-2013.

To discern significant changes in the trend and find the optimal number and location of places where a trend changes (National Cancer Institute, 2012), Joinpoint analyses were performed. The Joinpoint software version 3.5.3 was developed by the Surveillance Research Program of the United States National Cancer Institute and is based on the Poisson assumption. These analyses fit a multi-segmented model better compared with a simple linear regression model using a Monte Carlo permutation method (Kim et al., 2000; National Cancer Institute, 2012). The results of the joinpoint regression analysis are presented as annual percent changes (APC), as summary measures for the trends in CRC mortality rate.

We plotted age-specific CRC mortality rate by the time period and birth cohort as an exploratory analysis for the period and cohort effect. Then, based on the assumption that the number of deaths in each age group and period would be distributed as a Poisson variable, a log-linear model was performed to estimate the effect of age, period, and cohort as independent variables. To analyze the CRC mortality rate in an age-period-cohort model by sex, we selected the intrinsic estimator (IE) method proposed by Yang et al. (2008). The goodness-of-fit of the model was evaluated by the Akaike Information Criterion (AIC). After initial estimations of a series of Poisson log-linear models, we selected the IE to estimate the APC effects of CRC mortality.

Statistical analysis was performed by using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) and Stata version 12.0 (StataCorp LP, College Station, TX) software, using the "apc_ie" command statement. The software for the joinpoint analyses was the Joinpoint Regression Program version 3.5.3 of the National Cancer Institute.

Results

Table 1 presents the rates for age-specific mortality from CRC in Korean men and women. The CRC mortality rates have continuously increased among the 75-79 and 80+ age groups in men and the 80+ age group in women during the last three decades, whereas the decrease in mortality began in the younger age groups. In particular, in the youngest age group of 30-34, the mortality has decreased in both men and women since 1989-1993.

In the joinpoint analysis, changes in the linear trends were detected (Table 2). The CRC mortality rate of men increased significantly from 1984 to 2003 [APC: 7.5 (95%CI, 6.9 to 8.0)] and remained stable from 2003 to

Table 1. Age-specific Mortality Rate for Colorectal Cancer in Korea, 1984-2013 (100,000)

	Period of death					
Age	84-88	89-93	94-98	99-03	04-08	09-13
Men						
30-34	1.05	1.54	1.20	1.21	1.11	0.89
35-39	1.85	1.99	2.19	2.22	1.86	1.61
40-44	2.62	3.67	3.69	4.46	4.07	3.72
45-49	4.15	6.04	6.62	7.23	7.72	6.93
50-54	6.75	9.07	12.90	14.29	15.03	14.30
55-59	10.73	14.90	19.30	25.2	27.89	24.98
60-64	16.36	22.66	31.54	41.32	45.59	43.95
65-69	20.96	34.19	49.18	66.71	74.37	67.21
70-74	30.41	47.88	78.78	103.59	117.89	114.11
75-79	29.88	55.50	103.06	152.94	175.51	176.93
80+	28.65	63.82	101.66	209.62	264.45	300.25
Women						
30-34	0.79	1.40	1.34	0.94	0.95	0.98
35-39	1.65	1.59	1.98	1.85	1.55	1.67
40-44	2.47	3.31	3.78	3.51	3.34	2.89
45-49	3.41	5.65	5.75	5.92	5.88	5.31
50-54	5.15	7.06	7.83	9.50	9.65	9.16
55-59	6.54	10.65	13.72	15.19	15.54	12.86
60-64	10.13	13.76	18.90	21.25	23.22	20.71
65-69	12.36	19.93	28.94	35.51	36.35	31.13
70-74	15.02	29.45	45.25	54.77	58.62	50.65
75-79	18.57	33.89	61.57	83.65	93.90	88.72
80+	12.94	29.82	62.29	114.05	148.00	166.82

Table 2. Joinpoint Analysis for the Trends in Mortality of Colorectal Cancer by Sex

	ASR*		Joinpoint analysis†					
	Years		Trend 1		Trend 2		Trend 3	
	1984	2014	Years	APC	Years	APC	Years	APC
Overall	5.4	21.1	1984 to 1994	9.3 (8.0 to 10.5)	1994 to 2004	5.3 (4.5 to 6.1)	2004 to 2013	-0.9 (-1.4 to -0.3)
Men	7.0	29.1	1984 to 2003	7.5 (6.9 to 8.0)	2003 to 2013	-0.5 (-1.1 to 0.2)		
Women	4.4	15.2	1984 to 1994	9.6 (8.5 to 10.7)	1994 to 2004	4.3 (3.6 to 5.0)	2004 to 2013	-1.4 (-2.0 to -0.9)

*Age standardized incidence rate was calculated per 100,000 people for a given year and Segi's world standard population is used for age-standardization; †Joinpoint regression analysis was conducted to determine whether trends in incidence of colorectal cancer had changed significantly relative to sex from 1984–2013; ASR=Age-standardized incidence rate for a given year; APC=Annual percent change (95% confidence interval)

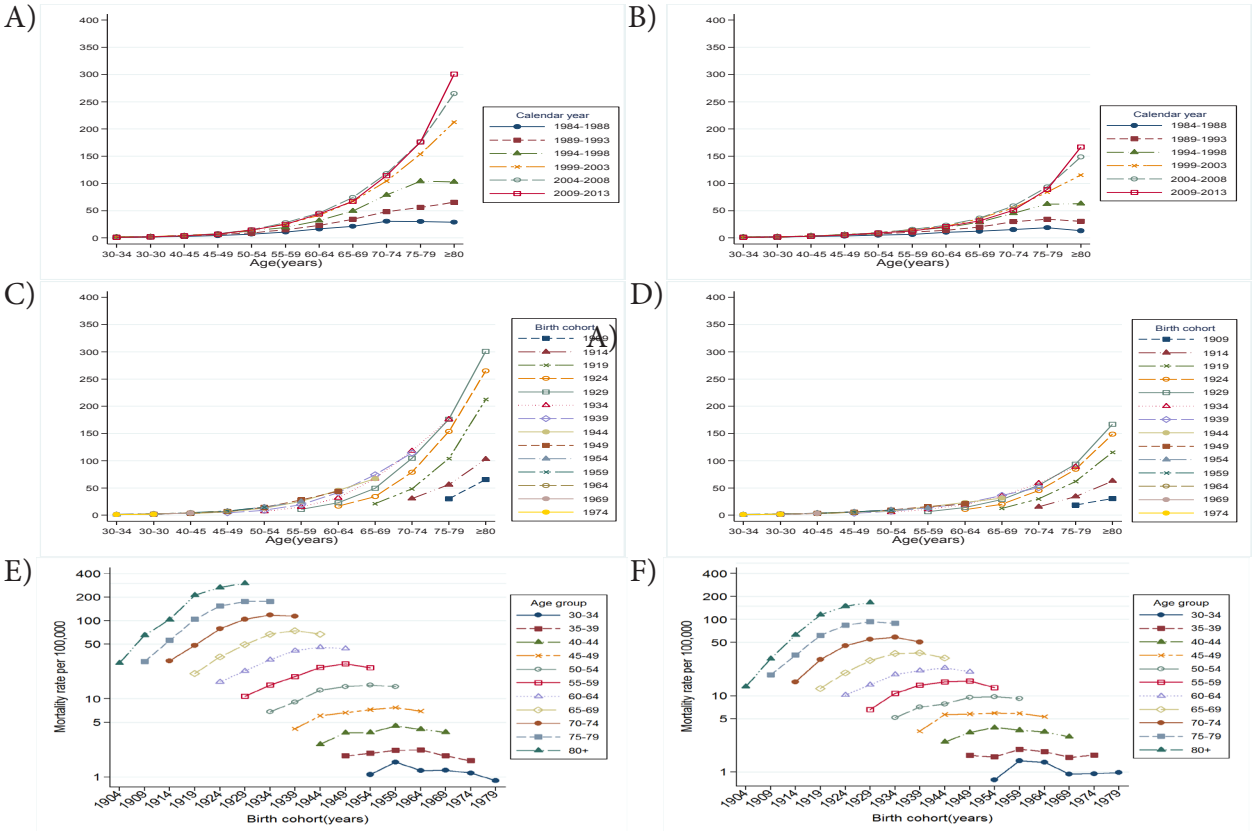

Figure 1. Age-Period-Cohort Effect of Age-specific Mortality Rate Caused by Colorectal Cancer from 1984-2013 in Males and Females. Age-specific mortality rate by period in men **A)** and women **B)**, Age-specific mortality rate by birth cohort in men **C)** and women **D)**, and birth cohort-specific mortality rate by age in men **E)** and women **F)**

Table 3. Goodness of Fit of Age-Period-cohort Model Assessment for Colorectal Cancer Mortality Rates in Korea, 1984-2013

Model	AIC	DEV	d.f.	ΔDEV	Δd.f.
Men					
APC	10.68	102.30	36	Reference	Reference
AC	19.03	661.52	40	559.22	4
AP	31.37	1495.51	50	1393.21	14
PC	11.01	141.78	45	39.48	9
Age	124.20	7632.21	55	7529.91	19
Women					
APC	11.17	147.02	36	Reference	Reference
AC	17.56	577.16	40	430.14	4
AP	40.16	2088.86	50	1941.84	14
PC	14.71	398.95	45	251.93	9
Age	111.83	6828.76	55	6681.74	19

*AIC: akaike information criterion; DEV: deviance; d.f.: degree of freedom; APC: full age-period-cohort model using intrinsic estimator model; AC: age/cohort model; AP: age/period model; PC: period/cohort model; Age: age model

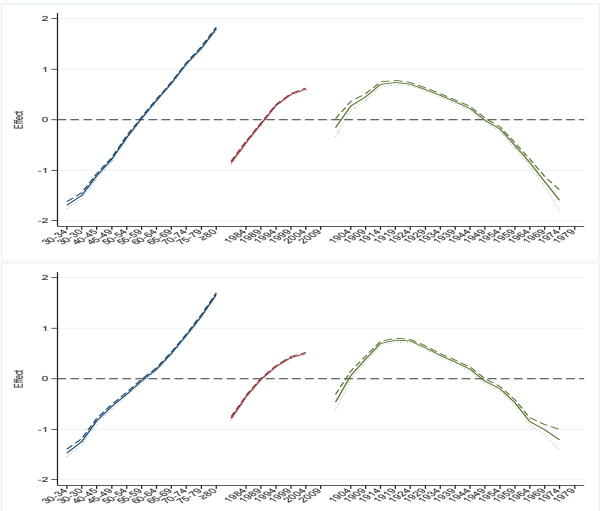

Figure 2. Age-Period-Cohort Analysis of Colorectal Cancer in Korean Men A) and Women B)

2013 [APC: -0.5 (95%CI, -1.1 to 0.2)]. In women, the CRC mortality rate increased sharply from 1984 to 1994 [APC: 9.6 (95%CI, 8.5 to 10.7)], and the rate of increase of CRC mortality slowed from 1994 to 2004 [APC: 4.3 (95%CI, 3.6 to 5.0)]. Since 2004, the CRC mortality rate of women showed a decreasing trend (APC: -1.4 (95%CI, -2.0 to -0.9)).

The age-specific CRC mortality rates in various time periods are depicted in Figures 1a and 1b. The increase in mortality associated with aging was more rapid among men than among women. The age-specific CRC mortality rate increased in both men and women in more recent years (Figures 1a and 1b). In the group of 75 years and older, CRC mortality rates were higher in the more recent birth cohorts (Figures 1c and 1d). Figures 1e and 1f also show that CRC mortality rates in older cohorts increased consecutively within the same age groups; however, birth cohort-specific CRC mortality rates have slightly decreased in younger birth cohorts within the same age groups.

Table 3 depicts the goodness-of-fit for the age-period-

cohort models. The age-period-cohort model using intrinsic model was the best fitted model to describe the trend in CRC mortality rate among both men and women.

The estimates obtained by the final APC model are shown in Figure 2. As expected, CRC mortality rapidly increased with age in both sexes. Among both men and women, the period effects also steadily increased and have slowed down since 1999. Among both men and women, the cohort effects were appreciably higher in the cohort born around 1919, then leveled off and declined in the younger generations.

Discussion

In this study, the CRC mortality rate has decreased in women since 2004 and remained stable in men since 2003. Our findings also showed that the change in CRC mortality rate trends in Korea have been affected by an underlying birth-cohort pattern. As expected, the CRC mortality rate rapidly increased with age in both sexes. Among both men and women, the period effects also steadily increased until approximately 2004, whereas the cohort effect curve showed decreasing patterns since the year 1919, which indicated the decreasing relative risk of CRC mortality in the recent birth cohort.

In the period 1999-2011, Korea showed a significant increase in CRC incidence among men and women (National Cancer Information Center, 2014), in agreement with early development and the process of westernized lifestyle factors associated with the development of CRC, such as alcohol consumption, obesity, cigarette smoking, and dietary habits (Shin et al, 2011; Shin et al., 2013). Changes in risk factors, particularly those related to lifestyle, have been suspected as the main contributors to the increase in colorectal cancer incidence (Shin et al., 2013).

In contrast with increasing incidence of CRC in Korea, our results revealed stable or decreasing trends in CRC mortality in recent years. Changes in CRC incidence are likely due to lifestyle factors, and decreasing mortality is due to earlier detection and improved treatment, especially among younger patients (van Steenbergen et al., 2009).

A similar pattern of CRC mortality has been observed in other Asian countries and is related to important advances in treatments implemented over the last few years (Shin et al., 2013). In particular, our study results were similar to those from a study in Spain (Ribes et al., 2009). In that study, during the period 1985-1994, CRC mortality increased in both sexes and increased in men and leveled off in women after 1995. These authors also reported that, in both sexes, there was an expected decrease in CRC mortality among people younger than 54 years old in the forthcoming 15 years. Among older people, a rise in CRC mortality in men and a leveling off of CRC mortality in women is expected.

Our study also showed that the change in CRC mortality followed decreasing birth cohort patterns. Similar decreasing birth cohort patterns for CRC mortality were reported in European countries and the United States. Based on population-based data from the Eindhoven Cancer Registry (ECR) in the southern Netherlands, it has been suggested that the increasing incidence and decreasing mortality in CRC is largely affected by birth cohort effects (van Steenbergen et al., 2009).

A study from population-based cancer registries in Spain also reported that changing patterns of mortality for CRC and the cohort effect for CRC incidence and mortality decreased in birth cohorts since those born from 1950 to 1960 (Abente et al., 2010). These phenomena suggest that CRC mortality was affected by improved accessibility to screening colonoscopy, stage shift of CRC cancer to the early stage due to increased early detection and advances in treatments.

A study in 6 European countries also showed that secular trends in CRC mortality increased in older cohorts born from 1800 to 1880 and decreased consecutively thereafter in both men and women (Sonnenberg et al., 2012). These birth-cohort patterns of CRC mortality suggest that the effects of enhanced screening colonoscopy examination and changes in other factors, such as a decrease in prevalence of Helicobacter pylori, may have affected the decrease in CRC mortality.

Additionally, it was reported that CRC mortality increased among elderly groups born before 1900 and decreased among elderly groups born after year 1900 in the United States. (Lee et al., 2013). This finding suggests that the CRC mortality already started to decrease before the introduction of screening tools such as colonoscopy. In Korea, it was reported that the prevalence of Helicobacter pylori showed a decreasing trend that was more pronounced in younger birth cohorts (Lim et al., 2013).

According to the annual report of national documents in the United States, the change in risk factors for CRC explained 35% of the decline in CRC mortality in the period 1975-2000, and screening for CRC explained 53% of the decrease in CRC mortality. Advanced treatments explained 12% of the CRC mortality reduction (Edwards et al., 2010).

In the present study, the decrease in mortality from colorectal cancer might be due to the widespread use of screening colonoscopy and sigmoidoscopy examinations (Suh et al., 2013) and partly due to a decrease in the prevalence of Helicobacter pylori infection (Wu et al., 2013; Lim et al., 2013) and smoking rate (Liang et al., 2009; Park et al., 2009).

However, the findings of some studies were different from our results. In an Argentinian study, the birth cohort effect reflected increasing tendencies among men but decreasing tendencies for women (Pou et al., 2009). In their study, the period effect also differed according to sex, with increasing or decreasing relative risk for males and females, respectively. Additionally, the cohort effect on CRC mortality in Taiwan is not consistent with our study (Su et al., 2012). In the age–period–cohort analysis, the estimated mortality rate increased steadily with age in both sexes. These authors also reported that changes in the patient sex ratio indicated an important etiological role of sex hormones, especially in women aged 60 years or younger. These different cohort effects may be partly due to different lifestyles, such as smoking or alcohol intake, and different screening strategies across the countries.

Some limitations should be considered in interpreting

our findings. First, improvement in the accuracy and completeness of CRC mortality data may lead to bias. However, if the accuracy and completeness of the CRC mortality data were improved, the change in CRC mortality would be underestimated. Second, because our analysis entirely relied on mortality data, we could not compare our data with other age-period-cohort analyses of CRC incidence. Third, our study was not an individual-based study; therefore, we could not investigate which factors contributed to the changes in CRC mortality. Despite these limitations, our study is a meaningful nationwide study to investigate the change in secular trends in CRC mortality and suggest strong birth cohort effects as determinants of change in CRC mortality trends in Korea.

In conclusion, our study shows that the CRC mortality rate increased in both men and women during the period 1984–2003, and thereafter, there were no more significant increases in the CRC mortality rate in men, and the CRC mortality rate in women has decreased since 2004. These changes in trends in CRC mortality may be explained by birth cohort effects, which suggest differences in colorectal screening, lifestyle factors and prevalence of infection by birth cohorts.

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