Association between Colorectal Cancer Screening Rate, Related Risk Factors and Mortality in Japanese Prefectures: An Ecologic Analysis Based on Prefecture Level Data

by

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Abstract

Background: Colorectal cancer (CRC) is still a major public health concern in Japan. This study aims to examine the association between the colorectal cancer screening rate, related risk factors, and mortality in Japanese prefectures.

Methods: This ecologic study used publicly available prefecture-level data related to CRC screening rate (SR), detailed examination rate, CRC risk factors i.e., smoking, alcohol, obesity, physical activity, diabetes, red meat, income, and the number of gastroenterologists and endoscopists, stage of colorectal cancer and mortality. Several cross-sectional time series datasets were created using SR data in 2007, 2010, 2013, and 2016 along with CRC risk factor data and other related data. Random effect linear regression analyses were performed with the age-adjusted mortality rate (AMR) of CRC as a dependent variable and SR and other CRC risk factors as independent variables.

Results: Prefecture-level panel data showed heterogeneity of CRC AMR. Mean plots of AMR across years showed a declining trend of AMR over the years. The SR showed a negative association (P<0.001, P<0.001, P=0.002 for 2007, 2010, and 2013), while alcohol consumption (P=0.024, P=0.006, P=0.038) showed a positive association and income (P<0.001, P=0.002, P =0.020) a negative association with CRC AMR based on all three-panel data sets. The detailed examination rate was significantly associated with CRC AMR in the 2007 and 2013 datasets (P=0.002, P=0.008), and the smoking rate in the 2010 and 2013 datasets (P=0.008, P=0.004).

Conclusion: CRC screening rate and several risk factors were significantly associated with CRC AMR in prefecture-level time series data.

Keywords: colorectal cancer, risk factor, screening rate

List of abbreviations

CRC	colorectal cancer
FOBT	fecal occult blood test
FIT	fecal immunochemical test
CS	colonoscopy
QI	quality indicator
SR	screening rate
T2DM	type 2 diabetes mellitus
AMR	age-standardized mortality rate
EC	estimated coefficient
SD	standard deviation

1. INTRODUCTION

1.1. Background Information

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the world, and Japan is one of the top three countries with the highest incidence and mortality of CRC(1). CRC screening programs using fecal occult blood tests (FOBT) and subsequent colonoscopy (CS) have been proven to decrease CRC mortality based on several large-scale randomized controlled trials (2) (3) (4) (5). Thereafter, a fecal immunochemical test (FIT) using an anti-human hemoglobin antibody was developed to overcome FOBT limitations. Several studies showing FIT effectiveness have been reported in Japan (6) (7) (8), and a population-based CRC screening program using FIT has been implemented in Japan since 1986. However, CRC is still the third and first leading cancer-related cause of mortality in Japan for males and females, respectively, in 2019.

There are several important quality indicators (QI) to implement effective CRC screening programs. Of them, the CRC screening rate (SR) is one of the important QI of CRC screening programs, and many studies have been conducted to increase SR(9). The other important QI is the detailed examination rate, which is equivalent to the proportion of participants who take CS after having a positive FIT result. If the detailed examination is low, the effect of CRC screening will be undermined (10) (11) (12). Both insufficient CRC screening uptake rate and the detailed examination rate are problems to be solved in Japan. The possible risk factors for CRC incidence in Japan include a family history of CRC (13), smoking (14), alcohol (15), obesity (16), physical activity (17), type 2 diabetes mellitus (T2DM) (18), and red meat consumption (19). Recently, research from Taiwan has reported the correlation between T2DM severity and long-term oncological outcomes of CRC. This study indicates the possible influence of CRC risk factors on CRC mortality. Although the QI of CRC screening programs and risk factors for CRC differ by prefecture, their influence on prefecture-level CRC mortality remains uncertain. Growing health-related variations by prefecture have also been reported in Japan (20); however, the influence of such variations on CRC morality has not been fully investigated. Of the socioeconomic status factors, income represents an economic status that may affect the treatment outcome. Endoscopists also play a key role in the management of CRC in real clinical settings; however, the distribution is uneven by prefecture. The influence of socioeconomic factors including variation in income and uneven distribution of endoscopists on CRC mortality remains unclear.

1.2. Objectives

This study aims to examine the association between geographic variations in CRC risk factors and prefecture-level CRC mortality in Japan using prefecture-level public data.

- Examine the heterogeneity of age-standardized mortality rates across Japanese regions by year.
- Examine the effect of the QI of the CRC screening program and risk factors for the age-standardized mortality rate of CRC using cross-sectional time series data
- Examine the effect of the QI of the CRC screening program and risk factors for the age-standardized mortality rate of CRC using cross-sectional data

2. METHODS

The less-than-75-year-old age-standardized mortality rate (AMR) by prefecture, other QI of the CRC screening program, and the risk factors for CRC by prefecture are collected using publicly available data. The items of QI included the screening rate and detailed examination rate. The risk factors included smoking, alcohol, obesity, diabetes, physical activity, T2DM, and red meat consumption, which were judged as probable or certain CRC risk factors in Japan. The evidence of those risk factors was based on the Development and Evaluation of Cancer Prevention Strategies in Japan by the National Cancer Center Institute for Cancer Control Project for Population Health Research. Other factors include income and stage of CRC distribution by prefecture and the number of gastroenterologists and endoscopists. The endoscopists in the present study represent "Board-certified Fellows of the Japan Gastroenterological Endoscopy Society."

Prefectures were divided into 8 regions. Hokkaido was included in the Hokkaido region. Aomori, Iwate, Miyagi, Akita, Yamagata, and Fukushima were included in the Tohoku region. Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, and Kanagawa were included in the Kanto region. Niigata, Toyama, Ishikawa, Fukui, Yamanashi, Nagano, Gifu, Shizuoka, and Aichi were included in the Chubu region. Mie, Shiga, Kyoto, Osaka, Hyogo, Nara, and Wakayama were included in the Kinki region. Tottori, Shimane, Okayama, Hiroshima, and Yamaguchi were included in Chugoku region. Tokushima, Kagawa, Ehime, and Kochi were included in the Shikoku region, and Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, and Okinawa were included in the Kyushu region.

2.1. Data source

2.1.1. Age-standardized mortality rate

The data of AMR by prefecture was obtained from Cancer Statistics. Cancer Information

Service, National Cancer Center, Japan. The model population by age in 1985 was used for reference. (https://ganjoho.jp/reg_stat/statistics/data/dl/en.html)

2.1.2. Screening rate and detailed examination rate.

The CRC screening uptake rate over 40 years and detailed examination rate were obtained from the Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan. (https://ganjoho.jp/reg_stat/statistics/stat/screening/dl_screening.html)

2.1.3. Smoking rate

Smoking rate by prefecture was obtained from the Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan. (https://ganjoho.jp/reg_stat/statistics/data/dl/en.html)

2.1.4. Alcohol consumption

Alcohol consumption data by prefecture was obtained from the national tax agency. (https://www.nta.go.jp/publication/statistics/kokuzeicho/tokei.htm) The data represented the sales volume of alcohol by prefecture. The value of alcohol consumption that was divided by the prefectural population was used for analysis.

2.1.5. Obesity

Obesity data were obtained from the results of the 2010 National Health and Nutrition Survey by the Ministry of Health, Labour and Welfare, which is listed in e-Stat. (https://www.e-stat.go.jp/stat-search/database?statdisp_id=0003234776) Body mass index ≥ 25 was used to define obesity in the present study (21).

2.1.6. Physical activity

Physical activity data were obtained from prefectural data listed in e-Stat. (https://www.e-stat.go.jp/regional-statistics/ssdsview/prefectures) These data represented the proportion of people who performed more than 10 minutes of physical activity in a week.

2.1.7. Type 2 diabetes mellitus

T2DM data by prefecture were obtained from the system of social and demographic statistics in Japan listed in e-Stat (https://www.e-stat.go.jp/regional-statistics/ssdsview/prefectures). T2DM data represented the estimated number of outpatient clinic diabetes mellitus patients. Since more than 90% of diabetes mellitus patients have T2DM in Japan (22), it was assumed that the data of diabetes mellitus patients represent the data of T2DM patients. The value of T2DM patients divided by the prefectural population was used for analysis.

2.1.8. Red meat consumption

Red meat consumption data by prefecture were obtained from the expenditure amount for red meat by prefectural capital in Japan listed in e-Stat (https://www.e-stat.go.jp/stat-search/files?tclass=000000330003&cycle=7&year=20220). The value of the expenditure amount for red meat divided by the prefectural population was used for the analysis.

2.1.9. Income

Income data by prefecture was obtained from the basic survey on wage structure conducted by the Ministry of Health, Labour and Welfare (https://www.e-stat.go.jp/stat-search/files?stat_infid=000040029286). The value of income represents the mean wage in June.

2.1.10. Gastroenterologists and Endoscopists

The data of gastroenterologists per prefecture was obtained from statistics for doctors, dentists, and pharmacists listed in e-Stat (https://www.e-stat.go.jp/stat-search/files?tclass=000001097738&cycle=7&year=20160). The number of endoscopists equivalent to “Board-certified Fellow of the Japan Gastroenterological Endoscopy Society” in the present study was obtained in response to an inquiry to the Japan Gastroenterological

Endoscopy Society and was divided by the prefectural population for the analysis.

2.1.11. Stage of colorectal cancer

The Stage of colorectal cancer was calculated based on the data from the Cancer Information Service, National Cancer Center, Japan. Annual Report of Hospital-Based Cancer Registries. (https://jhcr-cs.ganjoho.jp/hbcrtables/)

2.2. Dataset used in this study

The CRC screening uptake rates were only available for fiscal years 2007, 2010, 2013, 2016, 2019, and 2022. Since more robust evidence existed with CRC screening for decreasing CRC mortality compared to other risk factors, the datasets for analysis were designed based on the SR. Based on the previous research, it was assumed that a period of 5 years is necessary to manifest the influence caused by variations in variables in the present study (23) (24). Therefore, the four datasets were created for SR data 2007, 2010, 2013, and 2016. The AMR in 2012 and thereafter were used as dependent variables, and QI and risk factors of around 2007 were used as independent variables for the dataset 2007. The 2010, 2013, and 2016 datasets were similarly created. Therefore, the data sets 2007, 2010, and 2013 are constructed as panel data based on cross-sectional time series data on AMR, and the data set 2016 was constructed as one-year cross-sectional data.

Since not all annual year data for each variable were available publicly, the variable data closest to 2007, 2010, 2013, or 2016 were used in each dataset in case the data for those years were not available. Regarding the data on obesity by prefecture, which is available only for 2010, the one-year data was used for all 4 datasets. The years of raw data to set the four datasets analyzed in the present study are summarized in Table 1.

2.3. Statistical analysis

All statistical analyses were conducted using R (version 4.3.0). Analysis using multivariate random effects linear model was conducted using 2007, 2010, and 2013 data, where AMR was considered as dependent variables and other factors as independent variables. The univariate linear or multivariate linear regression was conducted using 2016 data. The multivariate linear regression analysis was conducted for the variables that had statistically significant estimated coefficients (EC) in univariate linear regression analysis. Further, forward and backward selection procedures were used for the model selection of multivariate linear regression using 2016 data. Correlations were analyzed by Spearman's rank correlation coefficient. All P-values were two-sided, and $P < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Japanese regional characteristics regarding age-standardized mortality rate and risk factors for colorectal cancers.

Japanese regional characteristics of 2016 data regarding age-standardized mortality rate and risk factors for colorectal cancers showed heterogeneity of CRC AMR and other risk factors across regions (Table 2). A numerically higher CRC AMR is observed in Hokkaido and the Tohoku region despite the fact that the screening rate that is important in the CRC screening program is the highest in the Tohoku region.

3.2. Analysis using 2007, 2010, and 2013 panel data

The conditioning plot divided by Japanese regions using 2007 data showed that heterogeneity of AMR existed both in prefectures and regions (Figure 1). The plot showed that the Kanto, Chubu, and Chugoku regions showed a relatively small range of AMR compared to other regions. Mean plots of AMR across regions using the 2007 data showed higher AMR in the Hokkaido and Tohoku regions compared to other regions. Further, Mean plots of AMR across years using 2007 data showed that AMR declined over the years (Figure 2).

The results of the random effects multivariate model analysis based on factors contributing to AMR using 2007, 2010, and 2013 data were summarized in Table 3. The 2007 data showed the EC of SR as -0.200, which is statistically significant (P<0.001). This means that every one-unit (%) increase in SR could result in a -0.200 decrease in the AMR of CRC holding other variables constant. Similarly, the EC of the detailed examination rate (EC: -0.039, P=0.002), alcohol consumption (0.026, P=0.024), red meat consumption (-0.0002, P=0.023), and income (-0.027, P<0.001) were observed as statistically significant.

The random effect multivariate model analysis using 2010 data showed that the EC of SR (-0.198, P<0.001), smoking rate (0.324, P=0.003), alcohol consumption (0.028, P=0.006), and income (-0.021, P=0.001) were statistically significant. The random effect multivariate model analysis using 2013 data also showed that the EC of SR (-0.129, P=0.002), detailed examination rate (-0.048, P= 0.008), smoking rate (0.303, P=0.004), alcohol consumption (0.037, P=0.038), and income (-0.020, P=0.020) were statistically significant. A summary of the significant variables in three-panel datasets is listed in Appendix A.

In the 2007, 2010, and 2013 datasets, the EC of the year was significantly lower in later years, which corresponded to the findings seen in the mean plots of AMR across years. The Tohoku region also showed significantly higher AMR in the three datasets compared to Hokkaido, which had the next highest AMR among regions.

3.3. Analysis using cross-sectional data of 2016

The analysis using cross-sectional 2016 data showed that the estimated coefficients of smoking rate (EC: 0.406, P<0.001), alcohol consumption (0.055, P=0.005), obesity (0.101, P=0.001), physical activity (-0.164, P<0.001), income (-0.015, P=0.024), and number of board-certified endoscopists (-1.670, P<0.001) were statistically significant. The EC of SR was not statistically significant (0.024, P=0.543). The multivariate linear regression analysis using the above 6 factors showed that the EC of smoking rate (0.220, P=0.018), alcohol consumption (0.041, P=0.017), and board-certified endoscopists number (-1.255, P=0.001) were statistically significant (Table 4). Stepwise model selection for the multivariate linear regression analysis showed that the EC of smoking rate (0.226, P=0.006), alcohol consumption (0.043, P=0.004), physical activity (-0.081, P=0.035) and board-certified endoscopists number (-1.279, P<0.001) were statistically significant (Table 5).

Figure 4 shows the correlation between AMR and the six factors that have significant EC in univariate analysis. Four of five prefectures in the Tohoku region are located on the upper left side when the correlation between AMR and the number of endoscopists in Japanese prefectures is observed individually (Appendix B). The negative correlation between AMR and the number of endoscopists is visually preserved after regional classification.

4. DISCUSSION

Since the present study was based on ecological design, no causal association can be assumed from the results; however, some of the results obtained offered us meaningful insights. The present study showed three important findings. Firstly, the effect of SR on the decrease in CRC AMR is observed consistently in the three-panel datasets. Secondly, heterogeneity of risk factors by prefecture was correlated with differences in CRC AMR between prefectures. Thirdly, social factors including income and the number of endoscopists were correlated with CRC AMR.

Although the effect of SR on the decrease in CRC AMR between prefectures was not observed in cross-sectional data, it was observed based on panel data. These results represent the fact that the effect of the CRC screening program is observed gradually over time, and a single-year AMR may be the result of SR over the years. The analysis based on cross-sectional data may have missed the effect of the CRC screening program. Panel data analysis is often conducted in a socioeconomic area. The analysis with panel data that includes time series data can be an effective method when conducting an ecological study to investigate the prefecture-level screening program effect in Japan. This type of study may also be applied to examine the effectiveness of other cancer screening programs. Although the strong assumption in the random effect model may become a bias and a limitation in the present study, the effect of SR is consistent in 3 datasets.

Some of the risk factors were significantly correlated with CRC AMR. Of these, SR, alcohol consumption, and income were consistently significant based on the three-panel datasets. Not all variables were consistently significant; however, the direction of the effect of risk factors was consistent with the expectation from previous research. Although both smoking and alcohol consumption are regarded as risks of CRC incidence, little is known regarding their role in CRC mortality. The increased mortality of other diseases including various cancers due to smoking and alcohol has been reported (25) (26). Nicotine, which is a major alkaloid content of tobacco, exerts an oncogenic effect through both receptor-mediated and non-receptor-mediated signalling processes, and it could also induce chromosomal abnormalities (27). Regarding acetaldehyde, which is produced by metabolism after ingesting alcohol, it is highly reactive with DNA and induces a genotoxic effect (28). These molecular-level effects may enhance cancer progression and lead to a poor prognosis. Previous systematic reviews and meta-analyses also showed that both preoperative smoking and alcohol consumption are correlated with increased postoperative complications (29, 30), which may result in higher mortality. These results from previous studies could support the findings of the present study.

The negative correlation between income and AMR was observed in all panel datasets and the cross-sectional dataset. The influence of socioeconomic status on CRC morality in

Japan has not been fully investigated. The higher income level may represent a financially stable condition that may motivate people to participate in the CRC screening program or to see doctors earlier. The possibility exists that higher CRC AMR may reduce wages; however, it seems less likely on a prefecture level. Although, Japan maintains a universal health insurance system and easy access to medical institutions for all citizens, a growing health disparity by prefecture has been reported (20). The results regarding income in the present study may represent a social determinant of health in Japan. The negative correlation between the number of endoscopists and CRC AMR is another important finding. Skilled endoscopists play a key role during the CRC management process since detection and diagnosis of CRC are done by endoscopists. A higher adenoma detection rate which is one of the quality indicators of endoscopists is associated with lower CRC morality (31). Therefore, the results obtained by endoscopists are acceptable to many clinicians; however, the causal relationship should be investigated further.

The mean plot showed the heterogeneity of AMR by year and prefecture. The declining trend of AMR is observed in the mean plots across years. The effectiveness of the policy and screening program for CRC is not enough; however, it demonstrated a consistent effect on AMR CRC. Increasing the SR is a key factor in decreasing CRC morality, and many studies have been conducted on it. Recently, the effectiveness of screening recommendations using the nudge theory to increase CRC SR has been reported in municipal-level research. The effectiveness of the reported nudge theory is certain, but small and generalizability is still not enough as it was only conducted in Tokyo city (32). It is necessary to develop additional screening recommendation methods. Further prefecture-level investigation is also necessary to rectify the geographic variation of CRC mortality.

5. Limitations

This study has several limitations. Firstly, the causal relationship between AMR and variables that were investigated in the present study cannot be determined due to the ecologic study design. However, the direction of significant EC was the same as expected. Our prefecture-level results support the previously published results. Secondly, it was impossible to obtain perfectly filled time-series data; therefore, substitution was conducted using closely observed data, which may decrease the quality of the analysis. However, since prefecture-level data will not change dramatically in a few years, we believe that the effect is not very impactful. Thirdly, sex difference was not considered in the analysis. Lastly, there is a possibility that the unobserved prefecture-level variables may correlate with the AMR, which could reduce the reliability of the random effects model.

6. Implications for Practice

The importance of SR in the CRC screening program is ascertained based on the results of the present study. Although the declining year trend of CRC mortality was observed based on prefecture-level data, CRC AMR is still high, and further countermeasures to raise SR and control risk factors should be considered. Uneven distribution of board-certified endoscopists by prefecture was also observed. The effect of this uneven distribution should be investigated. Based on further investigation, the redistribution or promotion of endoscopists in a high CRC AMR area should be discussed.

7. Conclusions

CRC screening rate was positively correlated with CRC AMR, and some of the risk factors including smoking and alcohol consumption were inversely correlated with CRC AMR in prefecture-level time series data. The influence of income inequality and the uneven distribution of board-certified endoscopists by prefecture on CRC AMR should be monitored and investigated further.

Table 1: The years of data used in the datasets in the present study

Variables	Data 2007	Data 2010	Data 2013	Data 2016
Age-standardized mortality rate	2012-2021	2015-2021	2018-2021	2021
Screening rate	2007	2010	2013	2016
Detailed examination rate	2008	2010	2013	2016
Smoking rate	2007	2010	2013	2016
Alcohol consumption	2007	2010	2013	2016
Obesity	2010	2010	2010	2010
Physical activity	2006	2011	2011	2016
Diabetes	2011	2011	2014	2014
Red meat consumption	2007	2010	2013	2016
Gastroenterologist	NA*	NA	2013	2022
Endoscopist	NA	NA	NA	2020
Stage of colorectal cancer	NA	NA	NA	2016

*NA, not applicable

Table 2: Japanese regional characteristics of 2016 data regarding age-standardized mortality rate and risk factors for colorectal cancers.

	Japanese regions							
	Hokkaido	Tohoku	Kanto	Chubu	Kinki	Chugoku	Shikoku	Kyushu
AMR, mean±SD (/10^5)	11.20±0.00	11.00±1.81	9.74±0.24	9.17±0.72	8.81±0.68	9.59±0.86	8.83±0.49	9.81±1.41
SR, mean±SD (%)	34.14±0.00	46.65±3.94	40.60±1.46	41.33±3.18	35.91±2.34	38.82±4.46	37.18±5.22	36.26±2.00
Detailed examination rate, mean±SD (%)	66.39±0.00	79.53±4.17	65.54±7.20	73.84±4.57	70.33±7.78	72.42±3.58	77.85±3.83	74.62±6.52
Smoking, mean ± SD (%)	24.70±0.00	21.57±1.52	20.80±1.20	19.49±0.77	18.39±0.91	18.44±0.43	18.03±0.78	19.39±1.33
Alcohol, mean±SD (kl/year/10^3people)	73.72±0.00	72.62±4.73	64.34±13.46	63.58±7.09	61.49±9.47	65.35±4.63	66.82±9.16	68.50±7.04
Obesity, mean±SD (%)	38.51±0.00	36.19±4.27	32.11±3.47	27.20±2.24	29.94±5.14	28.28±2.11	29.52±6.13	36.50±5.38
PA, mean±SD (%)	64.90±0.00	61.38±3.12	71.17±2.52	67.52±2.31	68.30±2.48	65.56±1.17	65.23±1.54	66.03±1.65
DM, mean±SD (%)	1.91±0.00	1.85±0.18	1.60±0.23	1.78±0.22	1.94±0.36	1.96±0.15	2.09±0.17	2.09±0.46
Red meat, mean±SD (1000 yen/person)	15.91±0.00	14.28±0.94	13.84±1.54	14.46±1.02	12.90±1.76	11.77±1.29	11.64±1.25	12.66±0.97
Income, mean±SD (1000 yen/month)	267.60±0.00	250.32±16.51	311.96±29.40	282.02±13.92	299.11±14.31	267.06±15.70	265.40±6.11	250.64±12.40
Gastroenterologist (/10^4 people)	1.40±0.00	1.26±0.18	1.03±0.26	1.09±0.20	1.36±0.21	1.38±0.12	1.31±0.07	1.45±0.25
Endoscopist, mean±SD (/10^4 people)	1.79±0.00	1.39±0.11	1.60±0.38	1.76±0.45	1.87±0.38	1.89±0.22	2.01±0.12	1.76±0.35
Stage, mean ± SD (%)								
Stage 0-I	48.57	47.38	46.75	47.10	48.18	47.32	40.23	41.58
Stage II-IV	51.43	52.62	53.25	52.90	51.82	52.68	59.77	58.42

SD, standard deviation; AMR, Age-standardized mortality rate; SR, screening rate; PA, physical activity; DM, diabetes mellitus;

Table 3: Results of the random effects multivariate model analysis of factors contributing to colorectal cancer age-standardized mortality rate using 2007, 2010, and 2013 data

	2007 data (n=470)		2010 data (n=329)		2013 data (n=188)	
Variables	EC (95% CI)	P value	EC (95% CI)	P value	EC (95% CI)	P value
Screening rate	-0.200***(-0.266- -0.133)	<0.001	-0.198*** (-0.266- -0.131)	<0.001	-0.129** (-0.210- -0.047)	0.002
Year						
2012	Ref.	Ref.	NA	NA	NA	NA
2013	-0.059 (-0.339-0.222)	0.683	NA	NA	NA	NA
2014	0.186 (-0.095-0.467)	0.194	NA	NA	NA	NA
2015	0.004 (-0.277-0.284)	0.980	Ref.	Ref.	NA	NA
2016	0.019 (-0.262-0.299)	0.897	0.015 (-0.258-0.288)	0.914	NA	NA
2017	-0.119 (-0.400-0.162)	0.407	-0.122 (-0.396-0.151)	0.380	NA	NA
2018	-0.250 (-0.531-0.031)	0.081	-0.254 (-0.527-0.019)	0.069	Ref.	Ref.
2019	-0.423** (-0.704- -0.143)	0.003	-0.427** (-0.700- -0.154)	0.002	-0.173 (-0.434-0.088)	0.194
2020	-0.454** (-0.734- -0.173)	0.002	-0.457** (-0.730- -0.184)	0.001	-0.203 (-0.465-0.058)	0.127
2021	-0.642*** (-0.923- -0.361)	<0.001	-0.646*** (-0.919- -0.372)	<0.001	-0.392** (-0.653- -0.130)	0.003
Regions						
Hokkaido	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tohoku	2.283** (0.701-3.865)	0.005	2.671** (1.111-4.232)	<0.001	4.327*** (1.968-6.687)	<0.001
Kanto	1.689* (0.191-3.186)	0.027	2.147* (0.677-3.617)	0.004	3.110** (0.914-5.306)	0.006
Chubu	0.406 (-1.098-1.910)	0.597	1.332 (-0.165-2.829)	0.812	2.523* (0.234-4.812)	0.031
Kinki	0.384 (-1.282-2.051)	0.651	1.072 (-0.623-2.766)	0.215	2.735* (0.154-5.316)	0.038
Chugoku	1.243 (-0.518-3.004)	0.166	1.730 (-0.042-3.503)	0.056	3.318* (0.660-5.976)	0.014
Shikoku	0.000(-1.798-1.798)	1.000	0.930 (-0.995-2.856)	0.343	2.881 (-0.133-5.895)	0.061
Kyushu	0.261 (-1.406-1.928)	0.759	1.029 (-0.614-2.673)	0.220	2.678* (0.250-5.106)	0.031

Detailed examination rate	-0.039** (-0.064- -0.015)	0.002	-0.024 (-0.050-0.003)	0.008	-0.048** (-0.084- -0.013)	0.008
Smoking rate	0.143 (-0.004-0.290)	0.057	0.324** (0.109-0.538)	0.003	0.303** (0.098-0.509)	0.004
Alcohol	0.026* (0.003-0.048)	0.024	0.028** (0.008-0.048)	0.006	0.037* (0.002-0.071)	0.038
Obesity	0.003 (-0.044-0.049)	0.912	-0.023 (-0.078-0.032)	0.411	-0.001 (-0.071-0.054)	0.784
Physical activity	-0.0004 (-0.081-0.080)	0.993	-0.043 (-0.133-0.046)	0.345	0.026 (-0.095-0.148)	0.671
Diabetes mellitus	-0.331 (-0.895-0.234)	0.251	-0.290 (-0.838-0.258)	0.300	-0.260 (-0.976-0.455)	0.475
Red meat	0.0002* (0.000-0.000)	0.023	-0.0008 (-0.000-0.000)	0.251	0.0001 (0.000-0.000)	0.094
Income	-0.027*** (-0.039- -0.014)	<0.001	-0.021** (-0.033- -0.008)	0.001	-0.020* (-0.038- -0.003)	0.020
Gastroenterologist	NA	NA	NA	NA	-1.106 (-2.249- 0.038)	0.058

EC, estimated coefficient; CI, confidence interval; NA, not applicable; Ref., reference

* p < 0.05, ** p < 0.01, *** p < 0.001

Table 4: Results of the univariate and multivariate linear regression analysis of factors contributing to colorectal cancer age-standardized mortality rate using 2016 data

Variables	Univariate analysis EC (95% CI)	P value	Multivariate analysis EC (95% CI)	P value
Screening rate	0.024 (-0.055-0.103)	0.543		
Regions				
Hokkaido	Ref.	Ref.		
Tohoku	-0.194 (-2.632-2.245)	0.873		
Kanto	-1.456 (-3.870-0.958)	0.230		
Chubu	-2.032 (-4.412-0.349)	0.092		
Kinki	-2.390 (-4.804-0.024)	0.052		
Chugoku	-1.613 (-4.086-0.861)	0.195		
Shikoku	-2.370 (-4.894-0.156)	0.065		
Kyushu	-1.389 (-3.784-1.006)	0.248		
Detailed examination rate	-0.010 (-0.336-0.359)	0.687		
Smoking rate	0.406*** (0.224-0.587)	<0.001	0.220** (-0.052-0.068)	0.018
Alcohol consumption	0.055* (0.018-0.092)	0.005	0.041** (0.040-0.400)	0.017
Obesity	0.101** (0.041-0.160)	0.001	0.008 (0.008-0.074)	0.791
Physical activity	-0.164*** (-0.257- -0.072)	<0.001	-0.074 (-0.203-0.056)	0.256
Diabetes mellitus	-0.537 (-1.656- 0.583)	0.339		
Red meat consumption	0.0001 (-0.000-0.000)	0.424		
Income	-0.015* (-0.027- -0.002)	0.024	-0.001 (-0.017-0.015)	0.895
Gastroenterologist	-0.863 (-2.308-0.582)	0.235		
Endoscopist	-1.670*** (-2.525- -0.814)	<0.001	-1.255** (-1.979- -0.530)	0.001
Stage				
Stage 0-I	2.075 (-4.992-9.142)	0.557		
Stage II-IV	-2.254 (-9.661-4.553)	0.473		

EC, estimated coefficient; CI, confidence interval; Ref., reference
* p < 0.05, ** p < 0.01, *** p < 0.001,

Table 5: Results of stepwise model selection for the multivariate linear regression analysis of factors contributing to colorectal cancer age-standardized mortality rate using data from 2016

Variables	EC (95% CI)	P value
Smoking rate	0.226** (0.068-0.384)	0.006
Alcohol consumption	0.043** (0.015-0.071)	0.004
Physical activity	-0.081* (-0.156- -0.006)	0.035
Endoscopist	-1.279*** (-1.973- -0.585)	<0.001

EC, estimated coefficient; CI, confidence interval
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

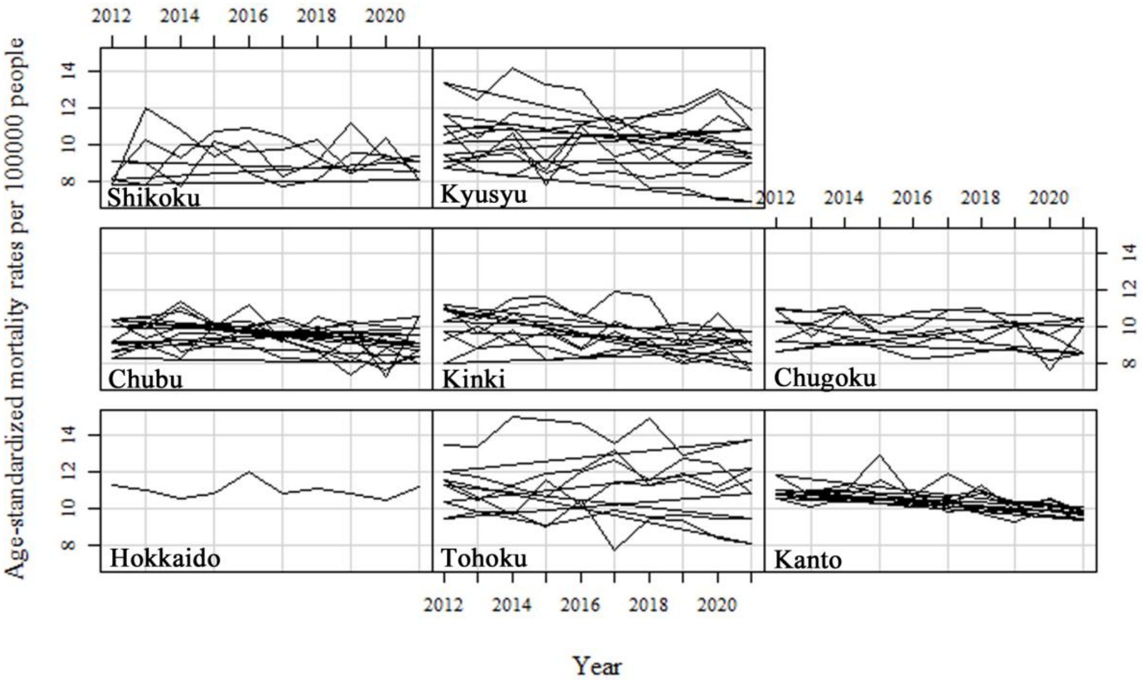

Figure1. Conditioning plot of AMR and year using the 2007 data according to Japanese regions.

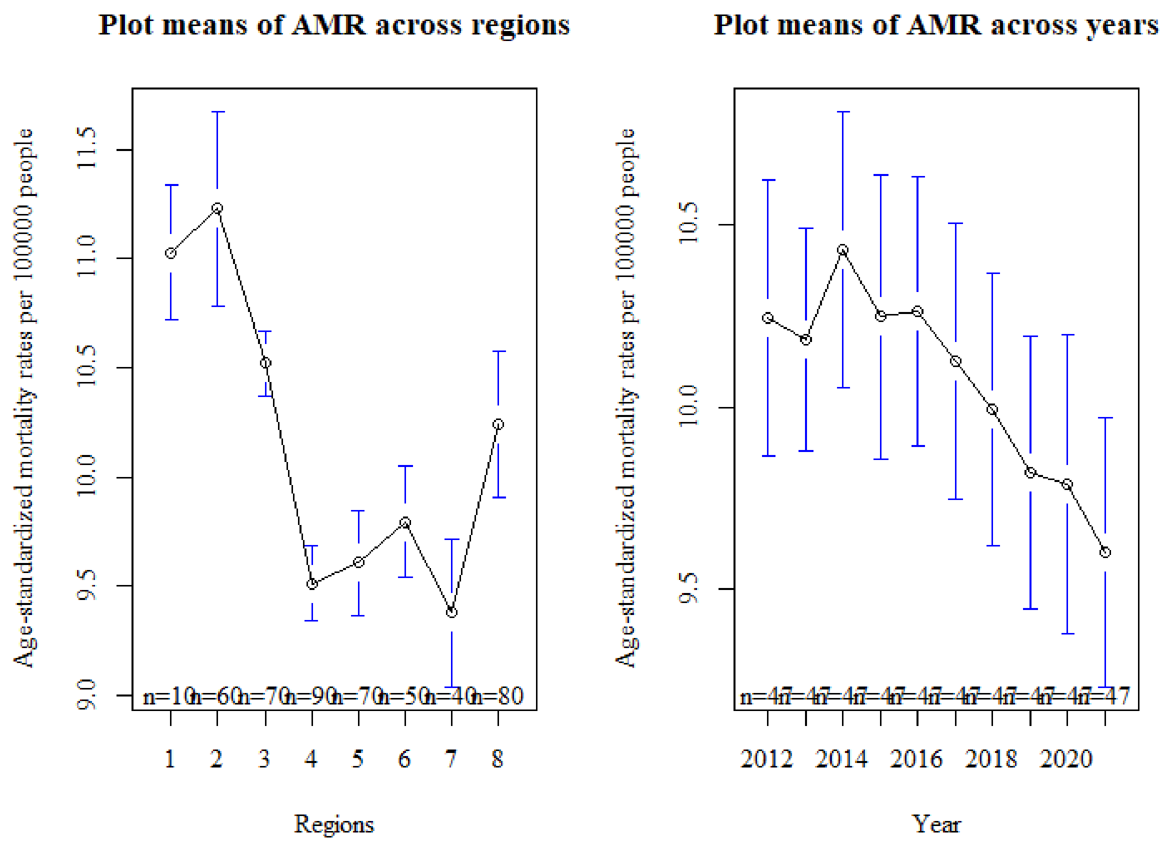

Figure2. Mean plots of age-standardized mortality rate across regions using 2007 data. AMR, age-standardized mortality rate across regions. 1, Hokkaido region; 2, Tohoku region; 3, Kanto region; 4, Chubu region; 5, Kinki region; 6, Chugoku region; 7, Shikoku region; 8, Kyushu region

n, number of prefectures

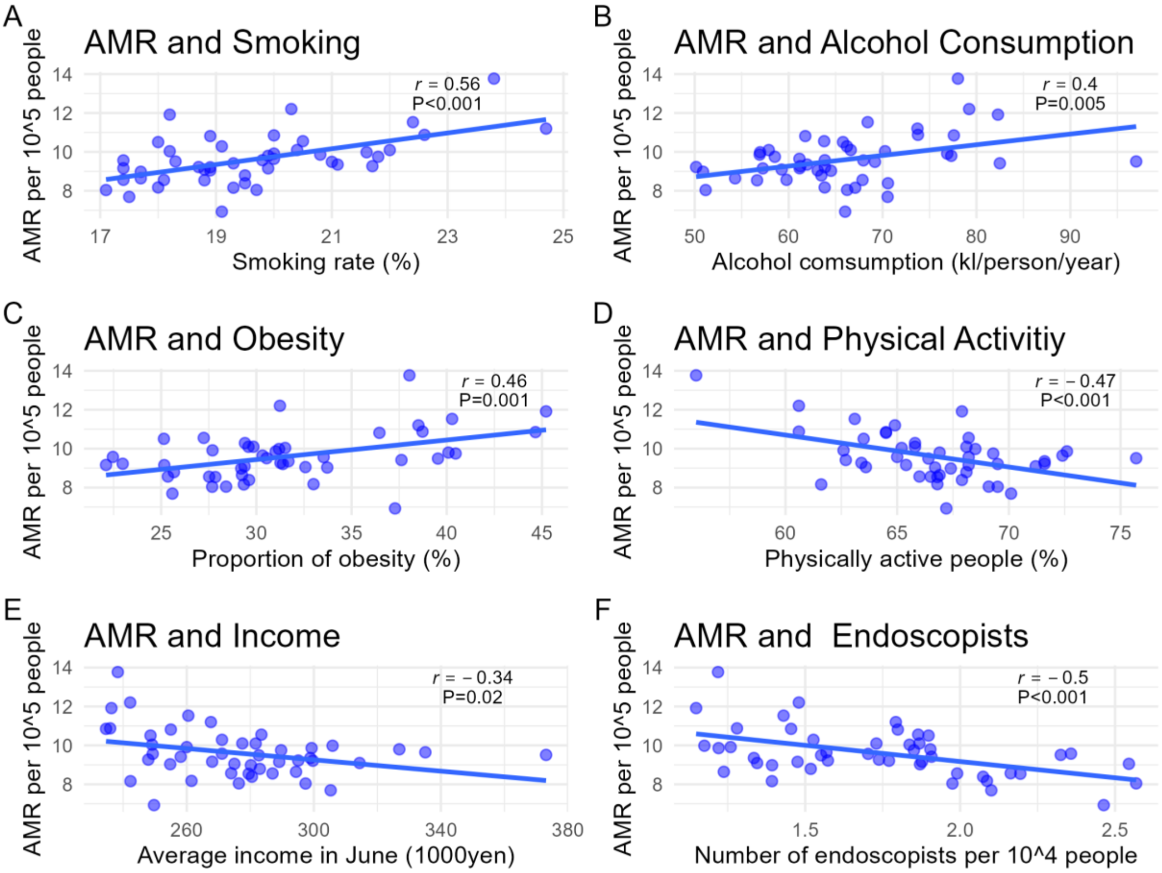

Figure3. The scatter plot with linear regression line and correlation coefficient between age-standardized mortality rate and risk factors that that have significant EC in univariate analysis using 2016 data. AMR, age-standardized mortality rate across regions

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Appendix A: Summary of significant variables in three-panel datasets.

	2007 data	2010 data	2013 data
Screening rate	Significant	Significant	Significant
Detailed examination rate	Significant	N.S.	Significant
Smoking rate	N.S.	Significant	Significant
Alcohol consumption	Significant	Significant	Significant
Red meat consumption	Significant	N.S.	N.S.
Income	Significant	Significant	Significant

N.S., not significant

Appendix B: The correlation between age-standardized mortality rate and the number of board-certificated endoscopists classified by Japanese regions. AMR, age-standardized mortality rate across regions