Stomach, Esophageal, and Lung Cancer Mortality Risk and Their Shared Risk Factors in Iran: A County-Level Spatial Analysis

Abstract

Background: Disease mapping has a long history in epidemiology. Evaluating the spatial pattern of several diseases, as well as shared and specific risk factors in mortality, is considered one of the applications of disease mapping. Stomach, esophageal, and lung cancers are among the five most common cancers among both genders in Iran. The present study aimed to investigate the geographical distribution of the relative risk of mortality and to define the spatial pattern of shared and specific risk factors for the three cancers mentioned above by sharing their mortality data at the province and county levels in Iran. Methods: In this ecological study, the mortality data of stomach, esophageal, and lung cancers were analyzed in Iran from March 2013 to March 2015. The Besag, York, and Mollie's (BYM) and shared component (SC) models were used to compare the spatial variations of the relative risks of those cancers by applying OpenBUGS version 3.2.3 and R version 3.6.3. Results: The number of deaths from esophageal, stomach, and lung cancers in Iran during March 2013-March 2014 was 11,720, of which stomach and lung cancers were 50% and 30%, respectively. In this period, stomach, esophageal, and lung cancer mortality rates were 9, 2, and 7 per 100,000 individuals, respectively. The spatial pattern of the stomach and esophageal cancer mortality was more similar to lung cancer due to the risk factors shared only between esophageal and stomach cancers. The relative risk for esophageal and stomach cancers was significantly higher in the northern half of Iran than in the southern half. However, the dispersion of the relative risk of lung cancer was higher than the other two cancers. The highest RR for esophageal, stomach, and lung cancers were in West Azerbaijan and East Azerbaijan provinces. The lowest relative risk for esophageal and stomach cancers was Hormozgan and for lung cancer was Ilam. Conclusion: Some differences were observed in the achieved patterns of provinces and counties, the most significant factor of which was related to considering smaller areas. As indicated in this study, high-risk areas can be identified easier by analyzing and mapping the diseases on a smaller scale and more accurate, less expensive, and faster health policies, and plans can be adopted to identify and reduce the risk factors related to diseases.

Keywords: BYM model, cancer mortality in Iran, shared component model, spatial pattern

Introduction

With a long history in epidemiology,^[1] disease mapping can identify risk factors and determine policies to reduce mortality by recognizing the spatial patterns and high-risk areas of disease in a population.^[2] Researchers have used univariate methods (single analysis for a single disease) and multivariate methods (combined analysis of several diseases) to estimate more accurate spatial patterns of diseases during the last few decades.^[3-5]

The spatial changes of diseases may be related to the differences in their risk factors. Disease mapping allows us to evaluate the hypotheses about the cause of diseases.^[3] In the beginning, only univariate methods were used for disease mapping. Then, the simultaneous statistical modeling of several diseases, causing the identification of their shared and specific risk factors and more accurate results than single analyses, was considered by researchers.^[6]

Evaluating the spatial pattern of several diseases, as well as shared and specific risk factors in mortality, is regarded as one of the applications of disease mapping.^[3,6,7]

Cancer is one of the main public health problems in the world^[8] and the second largest cause of mortality in Iran after cardiovascular problems.^[9]

Stomach, esophageal, and lung cancers are among the five most common cancers in Iran.^[9-11] Identifying high-risk areas and the spatial distribution of risk factors is one

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of the required strategies for controlling and implementing preventive policies to reduce the abovementioned cancers.^[12] The present study aimed to investigate the geographical distribution of the relative risk of mortality and determine the spatial pattern of shared and specific risk factors for the three cancers mentioned above by sharing their mortality data at the county level in Iran. For this purpose, the model introduced by Besag, York, and Mollie (BYM)[13] was used for analyzing each cancer and determining its spatial pattern. The BYM model is one of the most widely used disease mapping models where the spatial correlation of neighboring areas is considered. A hypothesis states that the areas close to each other behave similarly in relation to the disease.^[13] In addition, the shared component (SC) model^[4] was used for highlighting the similarity and nonsimilarity of spatial patterns of stomach, esophageal, and lung cancer mortality in the counties of Iran due to shared and specific risk factors. Such a model has been used in several studies for determining the spatial changes of risk factors in some diseases.^[7,14,15] In this model, latent variables are used as substitutes for risk factors.^[4,7] In the present study, the difference between counts of stomach, esophageal, and lung cancer mortality can be attributed to a shared risk factor (such as smoking[16-18]) and the other risk factor (such as nutritional factors^[16-18] that is shared only between esophageal and stomach cancer).

Based on the obtained data, no study was available on stomach, esophageal, and lung cancer mortality in Iran. Using data at the county level instead of the province level was one of the significant advantages of this study over other studies dealing with the geographical distribution of diseases in Iran. Thus, the present study aimed to evaluate the spatial variations in relative risk of stomach, esophageal, and lung cancer mortality in Iran and its relation to common risk factors between them. To this aim, the BYM and SC models were used to assess the spatial variations in the relative risk of stomach, esophageal, and lung cancer mortality.

Methods

Data

In this ecological study, the data on esophageal (ICD10 code C15), stomach (C16), and lung (C33-C34) cancer mortality in 30 provinces and 375 counties of Iran were considered during March 2013–March 2015 (information about Tehran and its counties is excluded(and were collected by the Network Management Center of Iranian Ministry of Health and Medical Education.^[19] The data included the count of deaths from stomach, esophageal, and lung cancer in different years and were classified based on province, county, gender, and age.

According to the previous study about risk factors of the esophagus, stomach, and lung cancers, we considered smoking as a common risk factor for these cancers

Model

Assume y_{ij} represents the number of deaths for the i-th county (i = 1,2,...,375) and the j-th cancer (j = 1,2,3). In addition, assume that y_{ij} has a Poisson distribution with parameters $E_{ij}\theta_{ij}$, where E_{ij} indicates the expected mortality rate in the i-th county due to the j-th cancer and represents a real relative risk (RR) unknown for the j-th cancer in the i-th county. The population at risk was used to compute the expected number of cases for each county and cancer. The population of each county in 1393 and 1392 was considered as a population at risk, which was estimated using the censuses of 1390 and 1395 and by calculating the population growth rate.^[20]

$$E_{ij} = n_{ij} \frac{\sum_{i} \mathcal{Y}_{ij}}{\sum_{i} n_{ij}}$$

where n_{ij} is the population at risk for the j-th cancer in the i-th region. Y_{ij} and E_{ij} are used as input information in fitting the models BYM and SC.

The BYM model was used for fitting the spatial pattern of each cancer. This model is one of the most widely used models in disease mapping where the spatial correlation structure of data is considered for obtaining more reliable estimates. In this structure, the data of neighboring counties are shared. In this structure, two counties that have at least one common border are considered neighbors. In the BYM logarithm model, the relative risk for the j-th cancer and the i-th county (θ_{ij}) is modeled as follows:

$$\log(\theta_{ij}) = \alpha_j + u_{ij} + v_{ij}$$

where α_j is the average mortality rate in all counties for the j-th cancer. For each cancer, u_i and v_i are the random variables being given in the model to consider structured and unstructured spatial changes. It is assumed that u_i follows a normal distribution with a mean equal to the average of the neighbor's number and variance inversely proportional to the number of these neighbors, and v_i has a normal distribution with mean zero and variance σ^2 .^[13]

Then, the Bayesian SC model was used to determine the distribution of risk factors.^[4] Based on the previous studies on the risk factors of esophageal, stomach, and lung cancers, smoking^[16-18] was considered in this model as a shared risk factor for the three cancers, and nutrition^[16-18] as a shared risk factor for both esophageal and stomach cancers. The SC model is a generalization of the BYM model, and one of its advantages is using latent variables as substitutes for risk factors without having relevant data.^[7,21]

Similar to the BYM model, it is assumed here that the risk logarithm is a function of random components:

 $log(\theta_{i1}) = \alpha_1 + us_i \times w_1 + ua_i \times \delta_1 + v_{i1}$ $log(\theta_{i2}) = \alpha_2 + us_i \times w_2 + ua_i \times \delta_2 + v_{i2}$ $log(\theta_{i3}) = \alpha_3 + us_i \times w_3 + v_{i3}$

where α_3 is defined as in the BYM model. θ_{i1} , θ_{i2} , and θ_{i3} represent the relative risk of esophageal, stomach, and lung cancer in the i-th county, respectively. u_{s_i} and u_{a_i} are the latent random variables being respectively substituted for the shared risk factor of three cancers (smoking) and the shared risk factor for esophageal and stomach cancers (nutritional factor), which both follow a normal distribution with a mean equal to the average of the neighbor's number and variance inversely proportional to the number of these neighbors.

w and δ are the unknown parameters being considered for estimating the effect of each risk factor on the relative risk of diseases and assuming that their logarithm has a normal distribution.

 v_{ij} represents the specific heterogeneity effects of disease and is included in the model to consider the probable changes that are not explained by the risk factors and are assumed to have a normal distribution.^[3,4] We repeat this process for provincial data. In this study, WinBUGS software version 1.4.3 and the MCMC method were used for obtaining the posterior distributions and estimates of parameters. In this method, the first 50,000 repetitions were discarded and then 2500 samples were stored at 80 repetitions. Algorithm convergence was evaluated using the Gelman–Rubin test.^[22] Finally, the maps were drawn using version 3.6.3 of R software.

Results

The number of recorded mortality due to esophageal, stomach, and lung cancers in Iran from March 2013 to March 2014 was 11,720, of which stomach and lung cancers were 50% and 30%, respectively. In this period, stomach, esophageal, and lung cancer mortality rates were 9, 2, and 7 per 100,000 individuals, respectively. The results of the BYM model for single analyses at the provincial and county level are presented in Figures 1 and 2, respectively. Northeastern and northwestern regions were at higher risk for esophageal cancer mortality. However, the risk of stomach cancer mortality was high in the northern and western regions. The dispersion of the relative risk of lung cancer mortality was higher than the other two cancers; other regions, except for the southeastern region,



Figure 1: Maps of the estimated relative risk in the BYM model for esophagus (a), stomach (b), and lung (c) cancer mortality at the provincial level in Iran



Figure 2: Maps of the estimated relative risk in the BYM model for esophagus (a), stomach (b), and lung (c) cancer mortality, at the county level in Iran

had almost an average risk. Single analysis maps indicated a shared spatial pattern for the relative risk of mortality by three cancers, especially in the northwestern and southeastern regions, which can be related to the shared risk factors between the three diseases. As observed, the similarity between the spatial pattern of the stomach and esophageal cancer mortality was higher than that of lung cancer due to the shared risk factors between esophageal and stomach cancers. The relative risk for esophageal and stomach cancers was significantly higher in the northern half of Iran than in the southern half. However, the dispersion of the relative risk of lung cancer was higher than the other two cancers.

Based on the spatial patterns obtained from the BYM model at the provincial level, Iran can be divided into two areas for mortality of esophagus cancer, in which the northern half exhibits a high risk while the southern half demonstrates a lower risk. In addition, we can observe a similar pattern for stomach cancer but with lower relative risk values. Estimating the effects of shared and specific risk factors for the studied cancers is mapped in Figures 3 and 4, respectively. Smoking changes were more than nutritional factors and had the highest effect in the

northwestern region and average effect in other regions except the southeastern regions. However, the effect of nutrition was significantly higher in the northern half than in the southern half. Accordingly, Iran was classified into two regions of low-risk and high-risk. The maximum effect of this factor was in the northeastern and northwestern regions and part of the north of Iran.

Table 1 indicates the relative weight of each risk factor derived from the SC model. The posterior mean of scale parameters is related to the shared factor of smoking $w_1 = 0.72$, $w_2 = 0.93$, and $w_3 = 1.47$. The

values
$$\frac{w_2}{w_1} = 1.29$$
, $\frac{w_3}{w_2} = 1.58$, and $\frac{w_3}{w_1} = 2.04$

indicated that the effect of smoking on stomach cancer is slightly more than on esophageal cancer, while its effect on lung cancer is more than on stomach and esophageal cancers. In addition, the posterior means for the parameters related to nutrition for esophageal and stomach cancers were obtained at 1.82 and 0.70, respectively. The available data indicated that esophageal cancer mortality was more affected by nutrition than stomach cancer mortality in Iran

$$(\delta_1 / \delta_2 = 2.6).$$



Figure 3: Shared risk in three cancers mortality (a) and specific risk for esophagus and stomach cancers (b) from SC model at the provincial level, in Iran



Figure 4: Shared risk in three cancers mortality (a) and specific risk for esophagus and stomach cancers (b) from SC model, at the county level in Iran

Table 2 provides the ranking according to the posterior means of RR of the provinces (each province includes several counties, as shown in Map 3) for each cancer. The highest RR for esophageal, stomach, and lung cancers were in West Azerbaijan and East Azerbaijan provinces. The lowest relative risk for esophageal and stomach cancers was Hormozgan and for lung cancer was Ilam.

Furthermore, Table 3 indicates the ranking of provinces based on the posterior mean estimated effect of the two risk factors. The highest ranking in the effect of smoking and

Table 1: Posterior median and 95% C1s for weights of three cancers in the shared component model										
Risk	Cancer	Coun	ty level	Province level						
Factors		Median	95% CI	Median	95% CI					
Smoking	Esophagus	0.72	0.43-1.23	0.97	0.50-1.91					
	Stomach	0.93	0.57 - 1.42	1.02	0.60 - 1.67					
	Lung	1.47	0.79-2.33	1.18	0.61-2.50					
Nutritional	Esophagus	1.82	0.90-3.20	2.27	0.99-3.57					
Factors	Stomach	0.70	0.36-1.27	0.75	0.37-1.51					

nutritional factors is related to West Azerbaijan and Ardabil provinces (northwestern Iran), respectively. The provincial and county divisions of Iran are shown in Figure 5.

Discussion

In this study, single analyses were used to obtain the geographical distribution of the relative risks for stomach, esophagus, and lung cancer mortality. Then, the SC model was used for evaluating the pattern of shared and specific risk factors for stomach, esophagus, and lung cancers. Estimating the effect of shared and specific risk factors on mortality, without having real data, is considered one of the features of the SC model with latent variables (as substitutes to risk factors).

Based on the results, the effect of the shared risk factor on lung cancer mortality was higher than on the other two cancers. It has a higher prevalence than the specific risk factor and has a high effect in other places except in southeastern Iran. The effect of the specific risk factor, which was considered as a shared risk factor between the

Table 2: Relative risk (RR) of esophagus, stomach, and lung cancer in Iranian provinces															
Province	RR	Esophagus				RR	Stomach				RR	Lung			
		Rank	High	Some	Low		Rank	High	Some	Low		Rank	High	Some	Low
			risk	risk	risk			risk	risk	risk			risk	risk	risk
Alborz	1.0	16		*		1.0	16		*		1.2	6	*		
Ardabil	1.1	13		*		0.8	19		*		0.5	28			*
Bushehr	0.2	27			*	0.5	25			*	0.9	17		*	
Chaharmahal Bakhtiari	0.1	29			*	0.9	17		*		0.7	24			*
East Azerbaijan	2.5	2	*			2.0	2	*			1.8	2	*		
Fars	0.3	23			*	0.7	22			*	0.8	21		*	
Gilan	1.1	11		*		1.4	6	*			1.2	4	*		
Golestan	1.3	8	*			0.8	21		*		0.7	25			*
Hamadan	0.6	20			*	1.1	12		*		1.1	10		*	
Hormozgan	0.1	30			*	0.3	30			*	0.6	27			*
Ilam	0.3	24			*	0.3	29			*	0.2	30			*
Isfahan	0.6	19			*	0.9	18		*		1.4	3	*		
Kerman	0.2	28			*	0.4	26			*	0.9	18		*	
Kermanshah	1.1	14		*		0.8	20		*		1.2	5	*		
Khorasan Razavi	1.7	4	*			1.3	8	*			1.0	11		*	
Khorasan North	2.1	3	*			1.3	9	*			0.8	23		*	
Khorasan South	1.5	6	*			1.0	14		*		1.1	9		*	
Kohgiluyeh Buyerahmad	0.2	25			*	1.0	15		*		0.6	26			*
Khuzestan	0.4	22			*	0.5	24			*	0.8	20		*	
Kurdistan	1.7	5	*			1.4	4	*			1.2	7	*		
Lorestan	1.3	9	*			1.2	10	*			1.0	16		*	
Mazandaran	1.3	7	*			1.5	3	*			1.0	12		*	
Markazi	0.6	18			*	1.3	7	*			1.2	8	*		
Qom	0.8	17		*		0.6	23			*	0.8	22		*	
Qazvin	1.0	15		*		1.1	11		*		1.0	15		*	
Semnan	1.2	10		*		1.0	13		*		1.0	14		*	
Sistan Baluchestan	0.2	26			*	0.4	28			*	0.3	29			*
West Azerbaijan	3.2	1	*			2.7	1	*			2.7	1	*		
Yazd	0.6	21			*	0.4	27			*	1.0	13		*	
Zanjan	1.1	12		*		1.4	5	*			0.8	19		*	

Table 3: The ranking of provinces based on the estimated effect of smoking and nutritional factors in Iran									
Province	Smoking			Nutritional Factors					
	Rank	High risk	Medium risk	Low risk	Rank	High risk	Medium risk	Low risk	
Alborz	9	*			17		*		
Ardabil	27		*		6	*			
Bushehr	21		*		28			*	
Chaharmahal Bakhtiari	20		*		27			*	
East Azerbaijan	2	*			2	*			
Fars	19		*		25			*	
Gilan	4	*			14		*		
Golestan	25		*		3	*			
Hamadan	7	*			19		*		
Hormozgan	28			*	30			*	
Ilam	30			*	18		*		
Isfahan	8	*			22		*		
Kerman	26		*		29			*	
Kermanshah	16		*		13		*		
Khorasan Razavi	10	*			4	*			
Khorasan North	17		*		1	*			
Khorasan South	14		*		8	*			
Kohgiluyeh Buyerahmad	18		*		26			*	
Khuzestan	24		*		23		*		
Kurdistan	3	*			7	*			
Lorestan	13		*		12		*		
Mazandaran	6	*			9	*			
Markazi	5	*			20		*		
Qom	22		*		16		*		
Qazvin	11	*			15		*		
Semnan	15		*		10	*			
Sistan Baluchestan	29			*	24			*	
West Azerbaijan	1	*			5	*			
Yazd	23		*		21		*		
Zanjan	12	*			11		*		

stomach and esophageal cancer mortality in this study, was higher than the effect of esophageal cancer on stomach cancer mortality.

The results indicated that the effect of specific risk factors on stomach and esophageal cancer mortality in the northern half of Iran was greater than in the southern half, and the relative risk of mortality in the southern half was more affected by the shared factor than the specific risk factor. East Azerbaijan and West Azerbaijan in northwestern Iran had a high ranking among the other provinces in terms of the effect of both risk factors. The abovementioned two provinces had high rates of mortality from the three cancers, which can be attributed to the interaction of shared rather than specific risk factors.

When the information is considered at smaller levels such as the county, high-risk areas can be identified more accurately. After that, the next studies can be focused on identifying risk factors in high-risk areas.

It is possible that regarding high levels such as the province leads to loss of information and makes it difficult to recognize whether the high risk is related to all parts of a province or a part of it. This information can be beneficial and informative for researchers and health policymakers.

The results obtained in this study are consistent with the results of previous studies.^[7,23-26] Mahaki et al.^[7] used the SC model to investigate the shared and specific risk factors for seven cancers at the provincial level. Although the present study had some similar results, it had some differences such as the distribution of smoking. As each province includes several counties, estimates of the relative risk of the provinces are strongly influenced by counties with very high relative risk or very low relative risk. In addition, the low consumption of fruits and vegetables was considered a shared risk factor for stomach and esophageal cancers, while most high-risk areas had appropriate and easier access to fruits and vegetables than other places, especially the deserts of Iran. Therefore, nutritional factors were considered as a shared risk factor for these two cancers. Nutritional factors such as the low consumption of fruits and vegetables,^[27,28] consumption of tea and hot food,^[28,29] consumption of salty foods,^[28,30] excessive consumption of



Figure 5: Counties and provinces in Iran

red meat,^[26,27] and Selenium deficiency^[29,31] can be regarded as one of the most significant factors in effective nutrition in the incidence of stomach and esophageal cancers.

The lack of reliable data at small levels such as the county level is the major limitation in Iran for disease mapping. As indicated, high-risk areas can be identified easier and better by analyzing and mapping the diseases on a smaller scale, and more accurate, less expensive, and faster health policies and plans can be adopted to identify and reduce the risk factors related to diseases.

Regarding the limitations of the present study, access to data about Tehran province was not plausible in this study. Thus, this province was excluded from the study.

Based on the obtained data, no study was available on stomach, esophageal, and lung cancer mortality in Iran. Using data at the county level instead of the province level in a multivariate spatial model was one of the significant advantages of this study over other studies dealing with the geographical distribution of diseases in Iran. Evaluating data at the county level provided more accurate and detailed data about their status than at the provincial level and could help in planning and making policies more effectively. Considering data on a larger scale sometimes ignores information at a smaller area and county level. In the present study, Isfahan province was identified as a low-risk province in terms of esophageal cancer mortality [Table 2], while Knorr and BayBank County in this province had very high esophageal cancer mortality.

Conclusion

The results of the present study show the importance of using data from smaller areas such as cities. by analyzing and mapping the diseases on a smaller scale scale, highrisk areas can be identified easier and better, and more accurate, less expensive, and faster health policies and plans can be adopted to identify and reduce the risk factors related to diseases. This requires data collection in small areas by healthcare systems.

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Conflicts of interest

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