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RESEARCH ARTICLE

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Exploring Spatial Patterns of Colorectal Cancer in Tehran City, Iran

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Abstract

Objectives: Colorectal cancer (CRC) may now be the second most common cancer in the world. The aim of this study was to determine whether clusters of high and low risk of CRC might exist at the neighborhood level in Tehran city. **Methods:** In this study, new cases of CRC provided from Cancer Registry Data of the Management Center of Ministry of Health and Medical Education of Iran in the period from March 2008 to March 2011 were analyzed. Raw standardized incidence rates (SIRs) were calculated for CRC in each neighborhood, along with ratios of observed to expected cases. The York and Mollie (BYM) spatial model was used for smoothing of the estimated raw SIRs. To discover clusters of high and low CRC incidence a purely spatial scan statistic was applied. **Results:** A total of 2,815 new cases of CRC were identified and after removal of duplicate cases, 2,491 were geocoded to neighborhoods. The locations with higher than expected incidence of CRC were northern and central districts of Tehran city. An observed to expected ratio of 2.57 ($p<0.001$) was found for districts of 2, 6 and 11, whereas, the lowest ratio of 0.23 ($p<0.001$) was apparent for northeast and south areas of the city, including district 4. **Conclusions:** This study showed that there is a significant spatial variation in patterns of incidence of CRC at the neighborhood level in Tehran city. Identification of such spatial patterns and assessment of underlying risk factors can provide valuable information for policymakers responsible for equitable distribution of healthcare resources.

Keywords: Colorectal cancer- spatial analysis- neighborhood- York and Mollie (BYM) spatial model- Tehran

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Introduction

Cancer is one of the most important causes of mortality and morbidity in the world. It is the third cause of death after cardiovascular diseases and traffic accidents in Iran. Annually about 70,000 new cases of cancer occurs in Iran (Gourabi, 2011). Among the types of cancers, colorectal cancer (CRC) is the second most common cancer in the world so that every year about one million new cases of this cancer are diagnosed in the around the world and about half of these cases are diagnosed resulted to death (Besag 1991; Stone et al., 2004).

According to report of International Agency for Research on Cancer (IARC), CRC is the fourth most common cancer after cancers of stomach, prostate and bladder in men Iranian with age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) 7.8 and 3.6 per 100,000 ; respectively. This type of cancer in women Iranian is the third most common cancer after breast and stomach cancer, with ASIR and ASMR 6.4 and 4.6 per 100,000 ; respectively. In general, the CRC is the third most common cancer in both sex after breast and stomach cancers with a proportion 7% of incidence rate and 7.6% of mortality rate of total cancers (Ferlay et al., 2015).

In Iran, the incidence of CRC in the elderly in compared to western countries is much lower, but its incidence is higher in the younger generation of the country which can be lead to considerable increase burden of disease in the future (Foroutan et al., 2008). From the other hand, the geographical distribution of CRC is not uniform in the country, so that Iran's major cities especially Tehran has always been one of the cities with the highest incidence of CRC (Ansari et al., 2006). The different study presented many risk factors (such as poor diet, low physical activity, being overweight, and smoking and alcohol consumption) for CRC incidence (Haggar and Boushey, 2009). Regardless of these risk factors, the various studies have shown that incidence and mortality of CRC can be associated with place and area based risk

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factors (DeChello and Sheehan, 2007; Shah et al., 2014). Locations is an significant factor in the epidemiology of diseases especially cancer because suitable information of different cancers in specific geographical areas can be help to planning health services for treatment and screening of high-risk groups (Babaei et al., 2005). In recent years researchers have very used of Geographic Information System (GIS) for identify geographical clusters of cancers especially CRC. Because GIS can be used in epidemiological researches for measurement of empiric data, identification of spatial patterns and understanding the relationships between diseases with other socioeconomic and environmental factors (Brewer, 2006; Barbara, 2008).

Many studies have be done about the spatial pattern of CRC in the world, But studies carried out in this field is limited in Iran, and the most of them also have been conducted only at the provincial level (Mahaki et al., 2011; Chamanparaa et al., 2015). However, examination spatial pattern of disease in finer geographic scale have some challenges that must be considered. The estimated rates and observed associations can be along with degree of bias due to spatial autocorrelation, population size heterogeneity and small area effect (Lawson et al., 2003). The Besag, York and Mollie (BYM) spatial model is used to offset these challenges with considering spatial autocorrelation and spatial heterogeneity among geographic units (Lawson et al., 2003; Pedigo and Aldrich, 2011).

Therefore ,given that the above explanation and also a lack of studies about spatial pattern of CRC in the neighborhood in Iran, the aim of this study was determination the smoothed standardized incidence ratio (SIR) and discovery of clusters of high risk and low risk of CRC incidence in the neighborhoods level of Tehran city by BYM spatial model.

Materials and Methods

The Study Area and Data collection

This retrospective study conducted in Tehran, Capital of Iran. The Tehran metropolitan area 638 square kilometer is situated on the southern slopes of the Alborz Mountains at a latitude of 35°45′N and a longitude of 51° 25′E. This city consisting of 22 municipal districts and also geographical unit of the study was 374 neighborhoods in Tehran city. In this study, total cases of incident CRC investigated during 2008 to 2011 in Tehran city. The information of these patients with home addresses extracted from Iran's cancer registry of ministry of health, then geocoded to neighborhood location. Also population of aged 55 and over for each neighborhoods extracted from national census 2006 and 2011.

Statistical analysis

Raw standardized incidence ratio (SIR)

The number of the observed cases in each neighborhood have a Poisson distribution

$O_i \sim \text{Poisson}(E_i\theta_i)$

So that O_i, E_i and θ_i represent the number of the observed cases, the number of expected cases and relative risk for neighborhood i; respectively. Expected cases is calculated as follows:

$$E_i = n_i \left(\frac{\sum_i y_i}{\sum_i n_i}\right), i = 1,2,\ldots . I$$

In the above formula, n_i is the number of population 50 years and over in neighborhood*i, y_i is the number of the observed cases in the neighborhood i. The standardized incidence ratio (SIR) is equal to the observed to expected ratio. The raw SIRs per neighborhoods were expected to be dispersed due to extra Poisson variability or over-dispersion. To deal with this problem, the York and Mollie (BYM) spatial model can be used for smoothed the raw SIRs.

*[(populaion in 2011+population in 2006)/2] → n_i is number of population aged 55 and over in neighborhood i

BYM model

When using of Poisson model for the count data in the spatial analysis, an important problem is Overdispersion or extra-Poisson variability. It occurs in the presence of spatial autocorrelation in the residual values which lack of attention to this problem can be lead to misleading results in the analysis. For deal with this problem Hierarchical Models such the Besag-York-Mollie (BYM) model is used (Pedigo and Aldrich, 2011). This model assumes that the number of cases of outcome is independent in each neighborhood and follows of the Poisson distribution. The BYM model was introduced by Kaldor and Clayton and was developed by Besag et al., (1991). This model in addition to of independent variables, it considers two sources of changes for the heterogeneity of incidence rate in every neighborhood, that these are v_i and u_i. The formula of BYM model is as follows:

$$\mathbf{Log}\,(\boldsymbol{\theta_i}) = \boldsymbol{\alpha} + \boldsymbol{u_i} + \boldsymbol{v_i} + \sum_{h=1}^{H} \boldsymbol{\beta i}\, \boldsymbol{x_{ih}}$$

In the above formula α is a log-relative risk baseline, v_i and u_i are random components of BYM Model and present Non-structural heterogeneity and structural heterogeneity; respectively. For variables of v_i and u_i are considered prior normal distribution and normal distribution of conditional autocorrelation; respectively. And also for β is considered prior normal distribution. Considering the distribution of conditional autocorrelation, the incidence rate in each neighborhood is dependent to the adjacent neighborhoods and it effected of incidence rate the neighborhoods (Lawson et al., 1999; Lawson et al., 2003). For more information, please refer to the article of Besag et al., (1991). In this study, we carry out Markov Chain Monte Carlo (MCMC) simulation for estimating the model parameters, then we run MCMC model with 100,000 iterations and the first 5,000 iterations ignored as burn-in. iterations started from over-dispersed initial values on four parallel chains. We used OpenBUGS version 3.2.3 for carry out the BYM model. (Kelsall and Wakefield, 1999; Lawson et al., 2003; Bilancia and Fedespina, 2009).

Identification of CRC clusters

The purely spatial scan statistic and discrete Poisson

model by using SaTScan software (v9.4.2) were used for determination of Neighborhood variation in incidence of CRC. For analysis, we need to the number of cases, the number of population and the geographical coordinates (longitude and latitude) by separating each neighborhoods. The standard purely spatial scan statistic creates a circular window (spatial cluster) on the map and then for comparing the number of disease cases in a geographic area (θ_{in}) with disease cases outside that area (θ_{out}) it moves throughout the study area. Since the result of the analysis may be sensitive to model parameters, especially window size, Gini coefficient is used for definition of the maximum spatial cluster. Indeed, for determination of the best collection and non-overlapping of clusters the Gini coefficient is more intuitive and systematic way (Han et al., 2016).

For cancer incidence, a Poisson model is typical model. The likelihood ratio statistic (LRS) of Poisson distribution (under test hypothesis; H_o: $\theta_{in} = \theta_{out}$; Ha: $\theta_{in} \neq \theta_{out}$) for a specific window is proportional to 1:

$$\left(\frac{c}{E[c]}\right)^{c}\left(\frac{C-c}{C-E[c]}\right)^{C-c}$$

In the above formula, c refers to the observed number of CRC cases within window, C presents the total number of CRC cases, and E[c] implies on crude expected number of cases within the window under the null hypothesis, C-E[c] is expected number of cases outside the window.

The randomization testing or Monte Carlo Hypothesis testing is used for statistical significance level of identified clusters because the exact distribution of LRS is unknown. The large number of random dataset are generated and the LRS value for each of random dataset is computed under null hypothesis. The Monte Carlo p-value of a window is computed as$(R_{beat}+1)/(R+1)$, so that R_{beat} shows the number of random dataset which its LRS is higher than LRS under real dataset and R is total number of random dataset. A window would be statistical significance at α=0.05 when it's LRS is higher than approximately 95% of LRS of random dataset. The windows with highest statistical significance likelihood ratio defined as most likely, secondary and tertiary cluster respectively. For statistically significant of Moran's Index and spatial clusters, *P*-value of < 0.05 using 999 permutations used. Sufficient statistical power was provided by with 999 replication in Monte Carlo simulation. The ArcGIS 10.3 software was used for all cartographic manipulations and displays.

Results

In total 2,815 new cases of CRC were identified in during March 2008 to March 2011 after removal of duplicate cases, that 2491 case of these had complete postal address and geocoded to neighborhood location. The minimum and maximum cases of CRC in the neighborhoods were 0 and 57; respectively. Figure 1 shows the number of observed cases of colorectal cancer

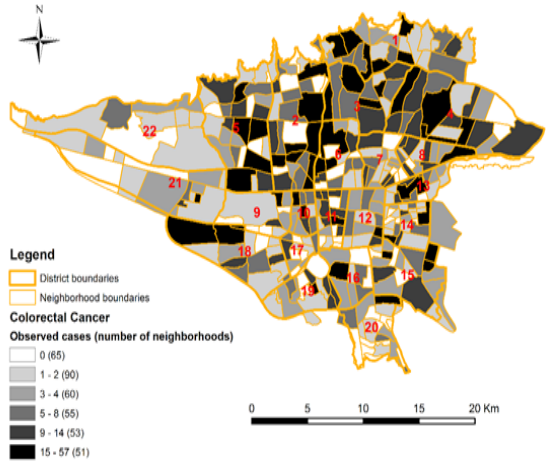

Figure 1. The Number of Observed Cases of Colorectal Cancer in the Neighborhoods of Tehran (2008-2011)

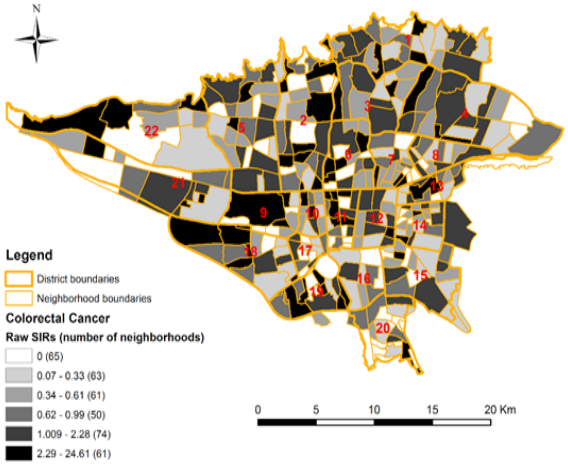

Figure 2. The Estimated Raw Standardized Incidence Ratio (SIR) of Colorectal Cancer Incidence in the Neighborhoods of Tehran (2008-2011)

Table 1. High and Low Risk Cluster for Colorectal Cancer (CRC) incidence Using by Spatial Scan Statistics in Tehran (2008- 2011)

Total CRC incidence (n=2,815)	Optimal Gini coefficient	MSC	Clustered detected	Involved District	At risk population	Observed cases (O)	Expected cases (E)	Annual cases per 100,000	O/E	RR**	p-value
Areas with high rates	0.354	0.03	Primary	2,6,11	38,038	152	59.05	129.6	2.57	2.68	<0.001
			Secondary	2,3	18,421	85	28.6	149.7	2.97	3.04	<0.001
			Tertiary	18,21	23,017	97	35.73	136.7	2.71	2.78	<0.001
Areas with low rates			Primary	4	36,175	13	56.16	11.7	0.23	0.23	<0.001
			Secondary	15	33,053	11	51.31	10.8	0.21	0.21	<0.001
			Tertiary	10,11,17	40,014	18	62.12	14.6	0.29	0.28	<0.001

MSC, maximum size cluster; **, Relative Risk is calculated as the observed divided by the expected within the cluster divided by the observed divided by the expected outside the cluster

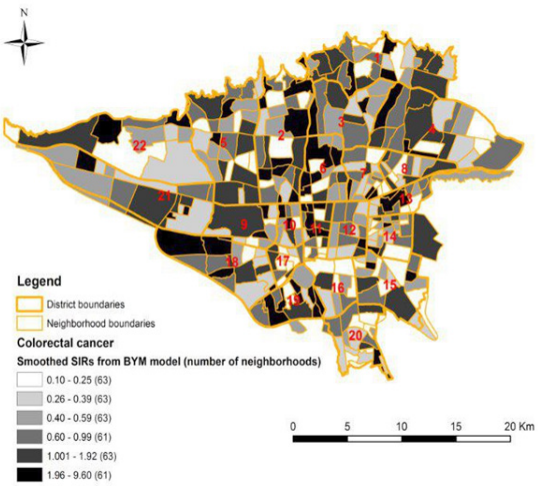

Figure 3. The Estimated Standardized Incidence Ratio (SIR) of Colorectal Cancer Incidence Using Besag, York and Mollie (BYM) Spatial Model in Tehran (2008-2011)

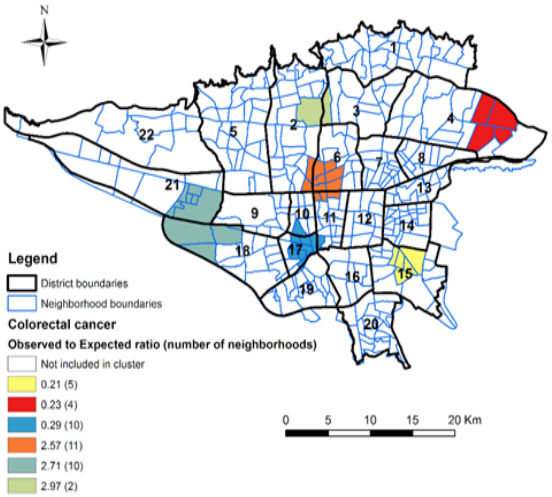

Figure 4. Spatial Clusters of Colorectal Cancer Incidence in the Neighborhoods of Tehran (2008-2011)

in the neighborhoods of Tehran, as that you have seen the majority of cases of CRC occurred in the northern and central areas of Tehran (Figure 1). In this study, The Moran's Index was 0.05 with *p*-value<0.05, as a result, the null hypothesis of zero spatial autocorrelation was rejected for all the neighborhoods.

Figure 2 shows the estimated raw SIR of CRC in neighborhoods of Tehran during 2008-2011. The variation range of estimated raw SIR was from 0 to 24.61. The value of raw SIR was 0 in 65 neighborhoods of Tehran, since there were no cases of colorectal cancer in these neighborhoods. In general, 36% of the neighborhoods had SIR higher than 1 and also 64% had SIR lower than 1 (Figure 2).

Figure 3 shows the estimated standardized incidence ratio (SIR) of colorectal cancer incidence using Besag, York and Mollie (BYM) spatial model in Tehran (2008-2011), as that have seen the results of two methods of raw SIR and BYM show that there is neighborhood inequality in incidence of CRC in Tehran city, so that the neighborhoods with higher than expected incidence of CRC located in districts of northern and central of Tehran city (Figure 2-3).

The geographic pattern of most likely clusters of CRC in neighborhoods of Tehran is depicted in Figure 4.The determined clusters of CRC incidence shows a statistical dispersion (Gini index=0.3540).The clusters with a higher than expected incidence were located in the northern areas, western and central city. The clusters with a lower than expected incidence were seen in the northeast and southeast areas of the city (Figure 4).

The specifications of most likely clusters of CRC in neighborhoods of Tehran can be seen in Table 1. The most likely cluster of higher than expected incidence CRC which was located in the northern areas, western and central city, with observed to expected ratio of 2.57 (p<0.001), including neighborhoods in districts of 2, 6 and 11. This means that the incidence of CRC is 2.57 times higher in this cluster compared to other area of city.

The most likely cluster of lower than expected incidence CRC which was located in northeast and south areas of the city, with observed to expected ratio of 0.23 (p<0.001), including neighborhoods in district of 4 . This means that the incidence of CRC is 0.23 lower within in this cluster compared to other area of city (Table 1).

Discussion

Different studies have examined the incidence cancer in Tehran by using pathology or the population based registry, however, this research is the first study of neighborhood based incidence CRC in Tehran city. The aim of this study was determination the smoothed standardized incidence ratio (SIR) and discovery of clusters of high risk and low risk of CRC incidence in the neighborhoods level of Tehran city by BYM spatial model during 2008 to 2011. Determination of clusters of diseases can be help in discovering the risk factors, visualizing patterns of distribution and potential disparities of diseases especially cancers, and finally in equitable allocation screening and early detection programs , as also equitable, palliative and therapeutic services for populations at risk in these clusters (Rassaf et al., 2012).

The results showed that the minimum and maximum cases of CRC in the neighborhoods were 0 and 57; respectively. The variation range of estimated raw SIR was from 0 to 24.61 and also 36% of the neighborhoods had SIR higher than 1. The results of two methods of raw SIR and BYM show that there is neighborhood inequality in incidence of CRC in Tehran city, so that the neighborhoods with higher than expected incidence of CRC located in districts of northern and central of Tehran city. The most likely cluster of higher than expected incidence CRC was located in the northern areas, western and central city, including neighborhoods in districts of 2, 6 and 11. The most likely cluster of lower than expected incidence CRC was located in northeast and south areas of the city, including neighborhoods in district of 4.

The results of this study showed that the most likely cluster of higher than expected incidence CRC was located in the northern areas, western and central city, including

neighborhoods in districts of 2, 6 and 11 with observed to expected ratio of 2.57 ($p<0.001$). Given that this is the first study of the spatial distribution of CRC incidence in the neighborhoods level of Tehran city and many other similar studies conducted have been in provincial levels and country in Iran (Larijani et al., 2004; Mosavi-Jarrahi et al., 2007; Rassaf et al., 2012; Chamanparaa et al., 2015), therefore previous studies were very limited at the neighborhood level, so that we found only one study that was conducted study by Rasaf, et al in this field, the aim of the study was to provide a disaggregated viewpoint on cancer incidence in all 22 districts of Tehran, using GIS, which its results showed the highest cancer incidence rates are in districts 6, 3, 1, and 2, whereas, the highest age specific rate (ASRs) found in districts 6, 1, 2, and 3. District 6 accommodated the highest ASRs in both the sexes (Rassaf et al., 2012). The results of this study were consistent with the results of our study. Generally, the northern areas, western and central of Tehran city have high-priced lands and expensive residential houses, In other words, Most of the population in these area have a high socioeconomic status. On the other hand, the various studies that have examined the association between socioeconomic status and CRC, have shown high levels of socioeconomic status is associated with progression of CRC (Le et al., 2008; Mohebbi et al., 2008; Haggar and Boushey, 2009). The reason for this problem may be due to the diet and lifestyle. Usually, the population with high socioeconomic status have high-fat diet and low-fiber diet, because an intake of fast foods, red meat and fried foods are more common in them. On the other hand also have less mobility that all these factors can be increase the risk of CRC (Navarro et al., 2004; Moshfeghi et al., 2011; Keyghobadi et al., 2013). Another reason for the higher incidence CRC in areas with higher socio-economic status may be due to more access to screening centers , the participate in screening programs and also followed by more cases of cancer be discovered.

The results of our study indicate that the most likely cluster of lower than expected incidence CRC was located in northeast and south areas of the city including neighborhoods in districts of 4, 11, 15 and 17. This area are populous and crowded with many types of low cost houses and flats. The most of the population have socioeconomic status of low to medium. A reason for the low incidence of CRC cases at these area can be due to lack of mass screening to detect CRC among the population (Elferink et al., 2012; Shah et al., 2014), As if regular screening programs implemented may increase the incidence of CRC cases in these areas.

This study had some advantages and limitations like other studies. The major advantage of this study could be that this research is the first study of neighborhood based incidence CRC to explore the spatial patterns of CRC at the neighborhoods level of Tehran city. This type of spatial analysis at the neighborhood level can provide valuable information for policymakers in the equitable distribution of healthcare resources in the neighborhoods level. The most important limitation of present study also was the incomplete and missing addresses of patients in cancer registry which this problem can cause some errors in the accurate estimation the results and create bias.

In conclusion, this study showed that there is a significant spatial patterns of incidence of CRC in Tehran city. Discovery and awareness of these spatial patterns can provide valuable information for policymakers in the implement of screening programs of CRC in the at-risk population and promotion of healthcare services to provide better treatment for CRC patients.

Conflict of interest

The authors have no conflicts of interest associated with the material presented in this paper.

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