

RESEARCH COMMUNICATION

Multivariate Disease Mapping of Seven Prevalent Cancers in Iran using a Shared Component Model

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Abstract

Background: The aim of this study was to model the geographical variation in incidence and risk factors of seven prevalent cancers in Iran. **Methods:** The data for cancers of esophagus, stomach, bladder, colorectal, lung, prostate, and female breast along with their risk factors in all 30 provinces of Iran for the year 2007 were included into study. Smoking, overweight, inadequate consumption of fruits and vegetables, socioeconomic status and low physical activity were studied as risk factors. Standardized incidence ratios were estimated using full Bayesian model. In addition, the shared component model was used to explore the spatial pattern of the cancers and to estimate the relative importance of their corresponding risk factors. **Results:** Fars and the Northwestern provinces were observed as high risk areas and Hormozgan (a Persian Gulf coastal province), Sistan and Baluchestan, South Khorasan, and Kerman provinces located in Southeast were areas of low risk for most cancers. For all five risk factors, larger effects on incidence of the relevant cancers were found in the Northern provinces compared to other areas. Smoking, overweight, inadequate consumption of fruit and vegetable, socioeconomic status, and low physical activity were found to have more effects on incidence of stomach, breast, esophagus, and breast cancers, respectively. **Conclusions:** Most of the high risk areas for seven cancers were in accordance with the results for spatial patterns of related risk factors and their relative weights on relevant cancers. The multivariate shared component model of the seven cancers achieves a considerable improvement in terms of Deviance Information Criterion over the individual modeling of diseases.

Key words: Cancer - prevalent sites - Iran - disease mapping - shared component model

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Introduction

Disease mapping has a long history in epidemiology and statistics and it may be defined as the spatial analysis, estimation and presentation of summary measures of health outcomes. The main aims of disease mapping are to: describe geographic variation of diseases risk, suggest possible risk factors that may explain variation (hypothesis generation), identify unusual high risk areas so that appropriate actions may be taken, assess health inequalities in order to better allocation of health care resources and finally construction disease atlas (Lawson et al., 2000; 2003).

As a first step to assess the status of geographic dispersion of disease rates, it is convenient to compute and map the Standardized Mortality Ratio (SMR) or Standardized Incidence Ratio (SIR) defined as the ratio

of observed to expected counts in each region (Tzala and Best, 2007). These unbiased estimators of relative risk are commonly used in disease map presentation but suffer from many drawbacks (Lawson et al., 2000; 2003).

To address the aspects of problems associated with SMRs a variety of alternative models have been proposed. Amongst them, Bayesian approach has an important role in modeling structurally complex data in spatial statistics. This approach consists of considering prior information on the variability of disease rates in the overall map, in addition to the observed events in each area. It can also take into account spatial correlation of disease rates among neighboring and geographical close areas (Lawson et al., 2000).

The issue of disease mapping has been developed considerably in recent years. These developments have focused mainly on the modeling of a single disease.

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However, there may be several diseases with common shared risk factors. Therefore it seems that identifying similar patterns for multiple diseases provide stronger evidence than that of separate univariate analyses (Dabney and Wakefield, 2005; Held et al., 2005; Dreassi, 2007). Multivariate disease mapping is defined as the joint modeling of the spatial occurrence of two or more diseases or of the same disease in two or more subsets of the population at risk (Tzala and Best, 2007; Dabney and Wakefield, 2005).

The potential benefits of a multivariate disease mapping include the ease of interpretation, improvement in the precision of the underlying disease pattern estimation, ability to identify shared and specific patterns of risk among different diseases and improvement in model evaluation criteria such as deviance information criterion (DIC) (Dabney and Wakefield, 2005; Held et al., 2005).

In the past decade, several approaches such as multilevel model for bivariate disease mapping, multivariate version of Besag, York and Mollie (MVBYM) model, polytomous logistic, proportional mortality and shared component model have been proposed to map diseases jointly (Knorr-Held and Best, 2001; Dabney and Wakefield, 2005; Dreassi, 2007). Among them, use of the shared component model has been increased considerably in recent years. In addition, there has been discussion in literatures on its feasibility, utility and applicability for different data structures (Dabney and Wakefield, 2005; Held et al., 2005).

In this study we apply the shared component model for joint modeling of the incidence rates of seven cancers and their five risk factors in Iran. Because of the inherent relationships between these cancers, we aimed at modeling jointly the incidence rates of these seven cancers in order to estimate and map their corresponding relative risks, detect the geographical variation, explore the patterns of spatial correlation and to estimate the relative weights of the risk factors for each cancer.

Materials and Methods

Data for seven prevalent cancers including esophagus (ICD10 code C15), stomach (C16), bladder (C67), colorectal (C18-C20, C26), lung (C34), prostate (C61) and breast (C50) cancer in 30 provinces of Iran in year 2007 were considered.

These are amongst the 10 most prevalent cancers in Iran and together account for approximately 50% of all cancers. Based on previous studies about possible risk factors of these cancers (Dehkordi et al., 2008; Montazeri, et al., 2008; Moradi, 2008; Malekzadeh et al., 2009; Moghimi-Hosseini et al., 2009; Hosseini et al., 2010; Shakhssalim et al., 2010), we considered smoking, overweight, low physical activity, inadequate consumption of fruits and vegetables as risk factors. All data have been collected and made available by the Iranian Ministry of Health and Medical Education (Iran

Cancer Registry Report, 2009; Iran Non-Communicable Diseases Risk Factors Surveillance Report, 2010). In addition, human development index (HDI) as a socioeconomic factor was taken from Statistics Center of Iran (SCI). It is a composition of education level, life expectancy and gross domestic product (GDP) for each province (Hermele, 2009; Islami, et al., 2009).

Smoking was calculated by multiplying the percentage of people who smoke tobacco in each province to the average number of smoked cigarette by them per day in that province. The overweight factor was defined as the percent of population with body mass index (BMI) ≥ 25 kg/m². People having activity less than 600 metabolic equivalent of task (MET) -minutes/week were considered as low physically active. Fruits and vegetables consumption was measured as the average number of servings per day.

Let O_{ij} shows the observed count for cancer site j ($j=1, \dots, 7$), grouped within province i ($i=1, \dots, 30$). The expected number of cases in each province (E_{ij}) was obtained by multiplying the national crude incidence rate and the estimate of the province population for year 2007. The latter was based on 2006 census conducted by SCI.

As an initial step, we assumed that the observed counts follow a Poisson ($E_{ij} \theta_{ij}$) distribution where θ_{ij} is the unknown true relative risk for cancer j in the province i . Its maximum likelihood estimate is $\hat{\theta}_{ij} = O_{ij} / E_{ij}$ known as standardized incidence ratio (SIR) which suffers from known drawbacks (Lawson et al., 2003; Lawson et al., 2000). To avoid these problems, we used the BYM model which yield more reliable estimates for relative risks for rare diseases or small areas by borrowing information from neighboring areas. In this model for relative risks, area-specific random effects are decomposed into a component u_i that takes into account the effects that vary in a structured manner in space (clustering or correlated heterogeneity) and a component v_i that models the effects that vary in an unstructured way between areas (uncorrelated heterogeneity). The uncorrelated heterogeneities are assumed to follow a normal distribution ($v_i \sim N(0, \tau^2)$).

For the clustering component, a spatial correlation structure is used, where estimation of the risk in any

Table 1. Shared Components and their Relevant Cancers

λ	Risk factor	Relevant Cancers (parameter)
λ_{1i}	Smoking	esophagus (θ_{i_1}), stomach (θ_{i_2}), bladder (θ_{i_3}), lung (θ_{i_4})
λ_{2i}	Overweight	esophagus (θ_{i_1}), colorectal (θ_{i_4}), prostate (θ_{i_6}), breast (θ_{i_7})
λ_{3i}	Inadequate fruit and vegetables	esophagus (θ_{i_1}), stomach (θ_{i_2})
λ_{4i}	HDI	esophagus (θ_{i_1}), stomach (θ_{i_2}), bladder (θ_{i_3}), colorectal (θ_{i_4}), lung (θ_{i_5}), prostate (θ_{i_6}) and breast (θ_{i_7})
λ_{5i}	Low PA	colorectal (θ_{i_4}) and breast (θ_{i_7})

area depends on neighboring areas. The conditional autoregressive (CAR) model (Besag et al., 1991) is used which, in simple formulation, specifies that the conditional distribution of each area-specific spatially structured component, given all other spatial effects, is a normal distribution with mean equal to the average of its neighbors, and variance inversely proportional to the number of these neighbors; the more neighbors an area has, the greater the precision is for that area effect.

Finally, for joint modeling the spatial distribution of incidence rates of the seven cancers, we used Bayesian shared component model (Held et al., 2005). The key idea in this model is the ability to include several spatial components (risk factors) that can be shared by a subset of diseases. These latent components act as surrogates for unmeasured risk factors. For each risk factor we will assign weights to determine the relative contribution of this component to each related diseases and represent variation in relevant disease (Held et al., 2005; Downing et al., 2008). In this application we included five shared components. These components and their relevant cancers were summarized in Table 1 (Moradi, A, 2008; Malekzadeh et al., 2009; Shakhssalim et al., 2010; Moghimi-Dehkordi et al., 2008; Montazeri, et al., 2008; Hosseini et al., 2009; Hosseini et al., 2010; Islami, et al., 2009).

Including these risk factors we can represent differences and variation in relevant cancers for each of them. Following Held et al (2005) and Downing et al (2008), our model for the log relative risk of the cancers is:

$$\begin{aligned}\log(\theta_{i1}) &= \alpha_1 + \lambda_{1i} \cdot \delta_{1,1} + \lambda_{2i} \cdot \delta_{2,1} + \lambda_{3i} \cdot \delta_{3,1} + \lambda_{4i} \cdot \delta_{4,1} + \varepsilon_{i1} \\ \log(\theta_{i2}) &= \alpha_2 + \lambda_{1i} \cdot \delta_{1,2} + \lambda_{3i} \cdot \delta_{3,2} + \lambda_{4i} \cdot \delta_{4,2} + \varepsilon_{i2} \\ \log(\theta_{i3}) &= \alpha_3 + \lambda_{1i} \cdot \delta_{1,3} + \lambda_{4i} \cdot \delta_{4,3} + \varepsilon_{i3} \\ \log(\theta_{i4}) &= \alpha_4 + \lambda_{2i} \cdot \delta_{2,2} + \lambda_{4i} \cdot \delta_{4,4} + \lambda_{5i} \cdot \delta_{5,1} + \varepsilon_{i4} \\ \log(\theta_{i5}) &= \alpha_5 + \lambda_{1i} \cdot \delta_{1,4} + \lambda_{4i} \cdot \delta_{4,5} + \varepsilon_{i5} \\ \log(\theta_{i6}) &= \alpha_6 + \lambda_{2i} \cdot \delta_{2,3} + \lambda_{4i} \cdot \delta_{4,6} + \varepsilon_{i6} \\ \log(\theta_{i7}) &= \alpha_7 + \lambda_{2i} \cdot \delta_{2,4} + \lambda_{4i} \cdot \delta_{4,7} + \lambda_{5i} \cdot \delta_{5,2} + \varepsilon_{i7}\end{aligned}$$

where $\theta_{i1}, \dots, \theta_{i7}$ represent the relative risk in province i for esophagus, stomach, bladder, colorectal, lung, prostate and breast cancer, respectively. α_j is the j th cancer specific intercept. Also, $\lambda_{11}, \dots, \lambda_{5i}$ show the shared smoking, overweight, fruits and vegetables consumption, socio-economic background and physical activity factors, respectively. The unknown parameters $\delta > 0$ are included to allow for different risk gradients of the shared components for the relevant diseases and ε_{ij} are the disease specific heterogeneous effects to capture possible variations not explained by the included terms in the model (Held et al., 2005; Downing et al., 2008).

In a Bayesian framework, all parameters or random effects are treated as unknown quantities and are thus given prior distributions. For the shared spatial random effects, λ_i it is reasonable to assume a spatially correlated prior distribution; we use an intrinsic normal conditional autoregressive (CAR) distribution with unit weight for

neighboring areas to capture local dependence in space. Since we used the CAR Normal prior, with sum to-zero constraints on the random effect terms, we assigned a flat prior on the cancer specific intercepts, α_j . For the logarithms of the scaling parameters, $\log \delta$ we assigned independent Normal prior distributions. The precision of the shared components, τ_1, \dots, τ_5 following were assumed to independently have a large variance gamma hyper-prior distribution. Finally the disease-specific heterogeneity terms, ε_{ij} were modeled to arise from a multivariate normal prior distribution with mean zero and a precision matrix P which was assigned a Wishart (Q,7) prior distribution, where Q is set to be a diagonal matrix with 1s (Downing et al., 2008; Best and Hansell, 2009; Onicescu et al., 2010).

The BYM and shared component model were fitted to the data using full Bayesian estimation using WinBUGS version 1.4.3 with the GEOBUGS version 1.2 add on. We monitored all fixed effects, weight and variance parameters for convergence. We used the Brooks-Gelman-Rubin diagnostic tool, which confirmed rapid convergence by 10,000 iterations and we based inference on a chain length of 10,000 after convergence (Spiegelhalter et al., 2002a). In the converged sample we evaluate the models fit using deviance information criterion (DIC). The DIC is defined as $DIC = \bar{qd}$ where \bar{q} is the posterior mean of the deviance and measures model fit; and q_d is the effective number of parameters in the model and measures model complexity. The DIC can be interpreted similarly to AIC (Akaike Information Criteria) but is appropriate for use with Bayesian hierarchical models. The lower the DIC value, the better the model fit (Spiegelhalter et al., 2002b). The DIC value of the joint modeling of the seven cancers using three shared components was compared to the sum of the DIC values from the seven individual BYM models. All maps were produced with the geographical information system (GIS).

Results

According to the Ministry of Health and Medical Education of Iran, a sum of 62037 cancers have been recorded between March 2007 and March 2008 in Iran, about 50 percent of which were due to seven cancers studied in this paper. The ratio of esophagus, stomach, bladder, colorectal, lung, prostate and breast cancers were computed as 5, 10, 2, 7.1, 7.7, 3.4, 5.1 and 11.5 percent, respectively.

Figure 1 shows the overall pattern of the relative risk estimates from the BYM model for each cancer. It can be seen that for esophagus and stomach cancers, areas of high risks were found in the Northern part of the country. For prostate and breast cancers the central and Southern provinces were the areas of high risks. For bladder and lung cancer, the areas of high risk were found in the Northwest and some provinces in the South. Areas of high risk for colorectal cancer were found in some

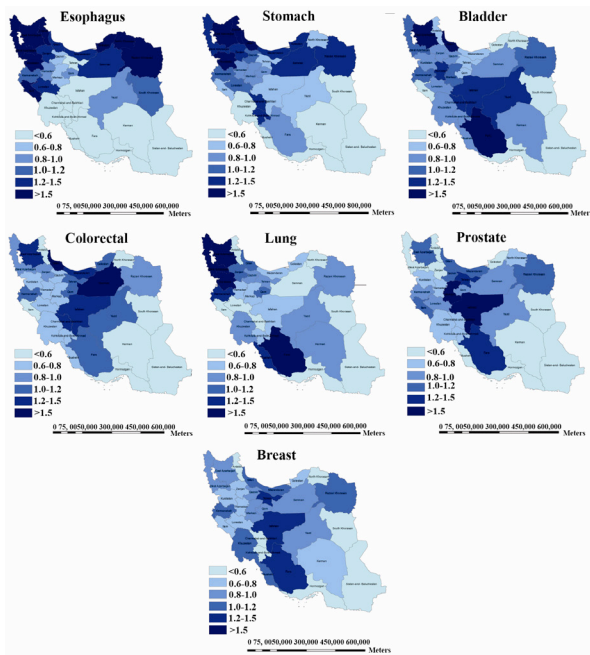


Figure 1. Maps of the Estimated Relative Risk in the BYM Model for Seven Cancers in Iran in 2007

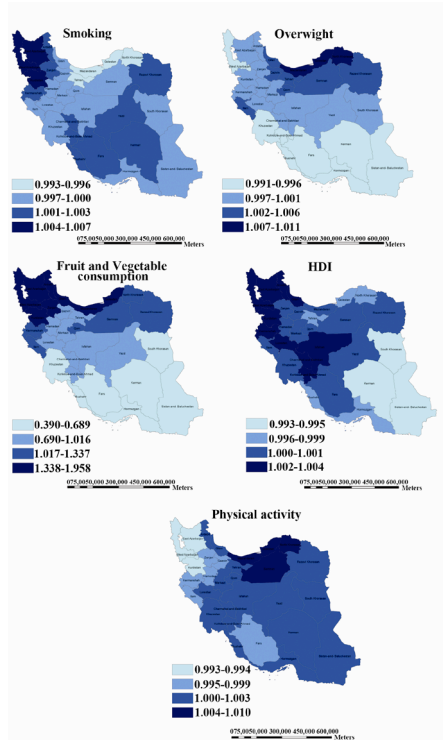


Figure 1. Maps of the Posterior Means of Five Shared Components using Quartiles in Iran in 2007

provinces in the North, center, south and Northwest of the country.

The estimates of the effects of the five shared components were also mapped in the Figure 2 using quartiles. According to the derived maps in this figure, the smoking risk factor had more effect in the northwestern provinces and less effect in the northeast. For overweight component the larger effects were found in northeastern provinces and the less effect were shown in southern part

Table 1. Posterior Median and 95% CIs for Weights of Seven Cancers in the Shared Component Model

Risk factor	Cancer	Median	95% CI
Smoking	Esophagus	1.060	0.457-3.302
	Stomach	1.005	0.442-2.068
	Bladder	0.970	0.435-2.110
	Lung	1.067	0.465-2.295
Overweight & Obesity	Esophagus	0.990	0.440-2.288
	Colorectal	1.008	0.457-2.162
	Prostate	1.017	0.458-2.191
	Breast	0.971	0.450-2.180
Fruit and vegetable consumption	Esophagus	1.322	0.593-3.753
	Stomach	0.783	0.389-1.792
Socioeconomic Background	Esophagus	1.081	0.443-2.163
	Stomach	1.159	0.484-2.270
	Bladder	0.924	0.454-1.886
	Colorectal	1.073	0.490-2.004
	Lung	1.013	0.453-2.279
	Prostate	1.002	0.472-2.131
	Breast	0.884	0.415-1.876
Physical activity	Colorectal	0.968	0.456-2.182
	Breast	0.993	0.441-2.122

of the country. The inadequate consumption of fruit and vegetable factor was the most varying in compare with other risk factors (relative risks from 0.390 to 1.958) and had the larger effect for the northern and northwestern provinces and less effect in the southern and eastern areas. For the HDI factor the more effect was found in the northwest and west of the country and less effect were shown in the east and southeast. The low physical activity factor had more effect in northeastern areas and less effect in the northwest.

Table 2 shows the relative weight, or level of importance, that each shared component has for the different cancers. The smoking component was more important for stomach and lung cancers than for the other relevant cancers. The effect of overweight factor was more for breast and prostate cancer than of esophagus and colorectal cancers. The inadequate consumption of fruits and vegetables had more effect on esophagus cancer relative to stomach cancer. The HDI factor had the most weight on stomach cancer and the least weight on breast cancer rather than other relevant cancers. The low physical activity component was more important for breast cancer relative to colorectal breast cancer.

The joint model had a DIC value of 1485.44 and the sum of the DIC values from the corresponding in the individual BYM models was 1688.66. This shows a great improvement in the DIC vales for the joint model. This improvement is a result of decreased posterior deviances (thus improved model fit) coupled with fewer numbers of effective parameters needed for joint modeling. This clearly indicates that in terms of DIC joint modeling of seven diseases has an advantage over modeling them individually.

Discussion

In this article, we fitted the shared component model introduced by Held et al (2005) to examine the joint spatial distributions of seven cancers incidence rates along with their related risk factors. We provided a description of the data sources, calculation of expected counts, and model structure, formulation and assumptions that can be used for planning of similar analyses.

In our study, the derived maps for estimated relative risks showed spatial differences in the incidence of seven cancers and demonstrated the areas of high risks. The results for all cancers were in correspondence to other previous studies about geographical pattern of these cancers in Iran (Sadjadi et al., 2003; Harirchi et al., 2004; Sadjadi et al., 2007; Azadeh et al., 2008; Farahmand et al., 2009; Mehrabani et al., 2009; Islami, et al., 2009). Fars and the northwestern provinces, especially East Azerbaijan shown to be the high risk areas for most cancers. Hormozgan, Sistan and Baluchestan, South Khorasan and Kerman provinces located in the Southeast were not seem to be areas of high risk for any cancer. Most of the high risk areas for seven cancers were in accordance with the results for spatial patterns of related risk factors and their relative weights on relevant cancers. Despite being high risk area for stomach, lung, prostate and breast cancers, the geographical patterns of their related risk factors were not in accordance in Fars province.

The shared component model considered all diseases rates as response variables in relation to latent risk factors. It has the prominent advantage that the latent components have a direct interpretation in terms of related risk factors which are shared by subsets of the diseases. This formulation also allows for the estimation of the weight of each component for each relevant disease, which shows the importance of the latent components for each disease. In addition to the ease of interpretation, in our application we showed that a joint model of the seven cancers achieves a considerable improvement in terms of DIC over the most common individual modeling of diseases, BYM. However, there are several limitations to our study that should be mentioned. The data on five rive risk factors are not available at individual level and we were forced to perform analysis in the province level and include these factors as covariates in the model, so the type of this study is ecologic in nature and, since ecological biases cannot be excluded, no definitive causal conclusions can be drawn and risk estimates seen at the area level may not reflect risk estimates at the individual level (MacNab Ying C, 2009). One constraint of this model is the fact that it assumes independency between the shared components, which may not be true in the real world and we cannot assess for the possible interactions among the covariates. Having missing neighbors for provinces that border other countries such as Iraq, Afghanistan and Pakistan is another limitation of this study which may happen in any other similar studies.

This phenomenon is called edge effect and could result in over or under-estimation. In addition, there may still remain other risk or confounding factors, and provincial differences which could be considered. Possible errors in non-communicable diseases risk factors surveillance can be considered as other limitation of our study. So, we should interpret the derived maps cautiously (Knorr-Held and Best, 2001; Held et al., 2005).

Since most cancers have a long latency period, with many years between any exposures to risk factors and diagnosis of disease, an important extension of this model can consider time dimension. Taking into account the possible difference of latency time between the exposure to risk factors and incidence of cancers would be another option (Clayton et al., 1993; Richardson et al., 2006; Tzala, 2004; Oleson et al., 2008). We are working on spatio-temporal disease mapping of these seven cancers in Iran using shared component model to show the temporal trend in addition to the spatial pattern of the diseases and to demonstrate feasibility and utility of the shared component model in multivariate temporal analyses.

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