Spatial analysis of stomach and liver cancers in California

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Background: The main purpose of this study was to explore the spatial distributions of relative risk in stomach and liver cancers, and to assess their associations with ecological risk factors, including % 1,2,3-trichloropropane (TCP) chemical in water above the maximum-allowed-level, poverty, rurality, gender, and race at county level in California, USA.

Methods: Separate Poisson-lognormal models were built for incidence of stomach and liver cancers over California counties. The study population were adults age from 20 to 79 years. During the study period, from year 2006 to 2015, 21,880 and 29,302 stomach and liver cancer incidences were included, respectively. The average yearly population over the decade was around 25,000,000. The Bayesian approach was used to explore the spatial distribution of the relative risk of stomach and liver cancers, respectively, adjusted by county level covariates mentioned above. Model selection was performed. Disease maps were produced for visualization.

Results: For both cancers, % rural area and % poverty were significant determinants. One unit increment of % poverty increased the relative risk of stomach and liver cancers by 1.3%, and 1.5%, respectively. One unit increment of % rurality decreased the relative risk of stomach and liver cancers by 0.5% and 0.2%, respectively. No statistical significance was found in the other variables. The estimated log relative risk for liver cancer was higher than stomach cancer. For stomach cancer, high relative risk area was found in the mid-western region; for liver cancer, high relative risk area was found from Bay area to northwestern region. In addition, the excess risks were found in Imperial county for both cancers.

Conclusions: The high-risk areas for stomach cancer were mid-western regions, for liver cancer were from Bay area and northwestern regions, and for both cancers were Imperial county. People lived in urban or poverty areas were at high risk for both cancers. The risk of liver cancer was higher. Our findings help public health officials identify higher cancer risks regions, and understand ecological risk factors to plan and target the use of resources.

Keywords: Stomach cancer; liver cancer; integrated nested Laplace approximation (INLA); Bayesian; disease mapping

Introduction

Cancer is the second leading cause of death, not only in the United States but also worldwide (1,2). Globally, stomach and liver cancers are listed in the most common causes of cancer death (2). In the United States, 35% of the patients who are diagnosed will die from the disease (3). According to the estimates by National Institutes of Health (NIH), in the year 2018, the incidence (the number of new cases) of stomach and liver cancers exceeded 26,000 and 42,000, respectively, while more than 10,000 and 30,000 patients died from stomach and liver cancers, respectively.

California, located in the west coastal region of the United States, is the largest state by population in the United States. It has had the highest rates of new stomach and liver cancers in the country since 1999 and 2004, respectively (1).

We explored impact of ecological risk factors associated with each cancer, including 1,2,3-trichloropropane (TCP) in drinking water, poverty, rurality, gender, and race (4-6). All variables above were measured at county level among 58 counties in California. Due to its intense agricultural use of the land and relaxed prior regulation on the releases of chemicals in the water aquifers, many California counties have been detected to have elevated levels of potent carcinogens in its wells and public water systems (7,8). One of the most toxic chemicals found was TCP, which, based on animal studies, has been shown to be associated with stomach, liver and other cancers in rats (9). No studies have discussed the association between stomach and liver cancers with the variable TCP in California. Among the demographic factors, we estimated the relationships between the area-level variables of percent below poverty level (poverty, %), percent of rural area (rurality, %), percent of males (male, %), and percent of African Americans (AA, %) with the incidence of stomach and liver cancers, respectively. Spatial variations of stomach and liver cancers have been found in some other geographical areas, including Ontario province in Canada, and Shenzhen, a major sub-provincial city in China (10-12), however, to date, spatial distributions of these two cancers have not been explored in California.

The purpose of this study was to assess, via a Bayesian analysis, the spatial distributions of relative rates for stomach and liver cancer and the associations of these diseases with TCP in drinking water, along with poverty, rurality, gender, and race. This county level risk estimation will help identify regions that may need targeted interventions designed to reduce the disease burden.

Methods

Data

Liver and stomach cancer incidence data from the years 2006 to 2015 were obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) from cancer registries in California (13). SEER is an authoritative source of information on cancer incidence and survival in the United States (14). The data were collected from population-based cancer registries (14). No obvious temporal pattern was detected in preliminary examination of the incidence for both cancers. As aggregating longitudinal data increase the capacity to detect spatial patterns, we included the total incidence in California at county level from the year 2006 to 2015 for each cancer separately. In order to calculate the age standardized incidence ratio (SIR), we considered three age groups: 20–39, 40–59, and 60–79 years. We used California population data from the same years as our outcome, 2006–2015, when calculating SIR. The population data were obtained from the United States Census Bureau (15). Also, several covariates were considered, such as percent of males (male), percent below poverty level (poverty), percent of rural area (rural), percent of African Americans (AA), and percent of TCP over the public health goal (PHG) level (TCP over the maximum allowed level) in each county in California. We assessed the percent of males from SEER (16). The percent of rural area was based on the 2010 census (17). The percent below poverty level and percent of African Americans was obtained from 2011–2015 American Community Survey 5-Year Estimates (15). The TCP test data through 2006–2018 was obtained from the drinking water programs of the California water boards which maintains the drinking water's quality analyses database (18). Only the active public water system and wells test results were included in our analysis. We used the allowed cutoff-PHG for TCP the cutoff (19). The percent of the allowed TCP was calculated as the percentage of test results in each county beyond established PHG cutoff of 0.0007 μg/L.

Statistical methods

Bayesian approaches offer natural framework for epidemiological studies, where the spatial distribution and determinants relating to health need to be considered (20). Due to the rapid development of computing, Bayesian approaches are now widely used. To reach the goal of disease mapping, spatial models which account for the spatial correlation between adjacent regions using random effects can be considered in the process of making inference. The random effects, including unstructured heterogeneity (UH) and structured heterogeneity (CH), can capture the spatial correlation not explained by the covariates. To capture the spatial correlated heterogeneity, a few models were used, such as the conditional autoregressive (CAR) model (21) and Besag, York and Mollie (BYM) model (22). By allowing each spatial area to have a different coefficient,

the model can also be extended in a geographically weighted regression (GWR) setting.

The purpose of this study was to explore the spatial distribution of the relative risk of stomach cancer and liver cancer respectively and related socioeconomic variables in 58 counties of California, USA, incorporating random effects. A Poisson-lognormal model used to fit each cancer type separately is given by:

$$Y_i \mid \beta \sim Poisson\left(E_i \theta_i\right) \qquad [1]$$

$$\log \theta_i = \alpha + \sum_{J=1}^{m} \beta_j x_{ij} + u_i + v_i \qquad [2]$$

$$E_i = \frac{\sum_{k=1}^{58} O_k}{\sum_{k=1}^{58} Pop_k} * Pop_i \qquad [3]$$

where y_i is the total number of the observed incidence of the stomach cancer or liver cancer considered in county i. θ_i is the relative risk and E_i is the expected incidence of the cancer considered in county i, which is the product of state incidence rate and county population (Pop_i). $i = 1,...,n$, $n = 58$ is the total number of counties. α is the intercept, and $\alpha \sim N(0, 0.005^{-2})$ distribution.

β_j is the coefficient for j^{th} covariate, $\beta_j \sim N(0, 0.005^{-2})$. The model was also extended in a geographically weighted regression (GWR) setting that local coefficients, β_{ij} represents the coefficient of jth covariate for i^{th} county, were estimated by introducing the neighboring features. $\beta_{ij} = \beta_j + \omega_{ij}$, where $\omega_{ij} \sim N\left(0, \tau_\omega^{-1} n_{\delta_i}\right)$, and $\tau_\omega \sim Gamma$ (0.001, 0.005). The random effect for the spatially correlated heterogeneity (CH), v_i, was assumed to follow a CAR prior:

$$v_i \sim N\left(\sum_{k \in \delta_i} v_k / n_{\delta_i}, \tau_v^{-1} n_{\delta_i}\right) \qquad [4]$$

Where δ_i represents the neighbor set in the ith county, n_{δ_i} represents the number of neighbors in the ith county and τ_v is a hyperparameter, where $\tau_v \sim Gamma$ (0.001, 0.005). u_i is the random effect for the uncorrelated spatial heterogeneity (UH), $u_i \sim N\left(0, \tau_u^{-1}\right)$, where $\tau_u \sim Gamma$ (0.001, 0.005). Separate models were fit for each type of cancer.

We performed sensitivity analyses and the results are robust for different specifications of the prior distribution parameters, for example *Gamma* (0.001, 0.001) and *Gamma* (1,1) for τ_v and τ_u, respectively.

Model selection

To measure the predictive accuracy of the fitted models, we considered the Watanabe Akaike information criterion

(WAIC) (23). WAIC is a fully Bayesian measurement (24) for estimating the out-of-sample expectation (25). The computation of WAIC starts with the computed log pointwise predictive density and then subtracts a correction for the numbers of effective parameters (26). The parameters degrees of freedom indicate the complexity of the model. As the deviance information criteria (DIC) is widely used in recent years, it was also included in the results for the purpose of comparison. A lower WAIC/DIC value indicates a better goodness-of-fit.

Computational approach and software

Integrated nested Laplace approximation (INLA) is a Bayesian inference approach proposed by Rue *et al.* (27) in latent Gaussian models via Laplace approximation. As an alternative of the traditional Bayesian analysis approach which uses Markov chain Monte Carlo (MCMC algorithms), INLA gains a much higher computation speed and accurate estimates (28). R-INLA is an ongoing development R package which provides a user-friendly interface, allowing users to perform inference based on the INLA method (29) through R command. Data preparation work was performed by using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software (30). The Bayesian analysis was implemented by the R-INLA R package. The graphical displays were using the R software (30).

Results

The *Figure 1A-1E* presents the spatial variation of the variables considered in California, including for TCP (range: 1–100%), percent of male (range: 47–68%), percent of poverty (range: 2–23%), percent of rurality (range: 0–45%), and percent of African American (range: 0–14%). The spatial variations of these variables look different to each other according to the maps. The *Figure 2A,2B* present the raw log SIR of the stomach and liver cancers respectively. The darker shades in the maps indicate higher SIR. The ranges of log SIR for stomach and liver cancer are (–∞, 0.51] and [–1.11, 0.23], respectively. For the SIR of stomach cancer, the SIR for 20 out of 58 counties was over 0, while for liver cancer it was 9 out of 58 counties. The counties with higher risk are located in the midwestern regions of the state for liver cancer.

Tables 1,2 include the measurements of goodness-of-fit for stomach and liver cancers, respectively. Models 1(a) and (b), 4(a) and (b), and 9(a) and (b) are the models without

A
TCP (%)

B
Male (%)

C
Poverty (%)

D
Rurality (%)

E
African American (%)
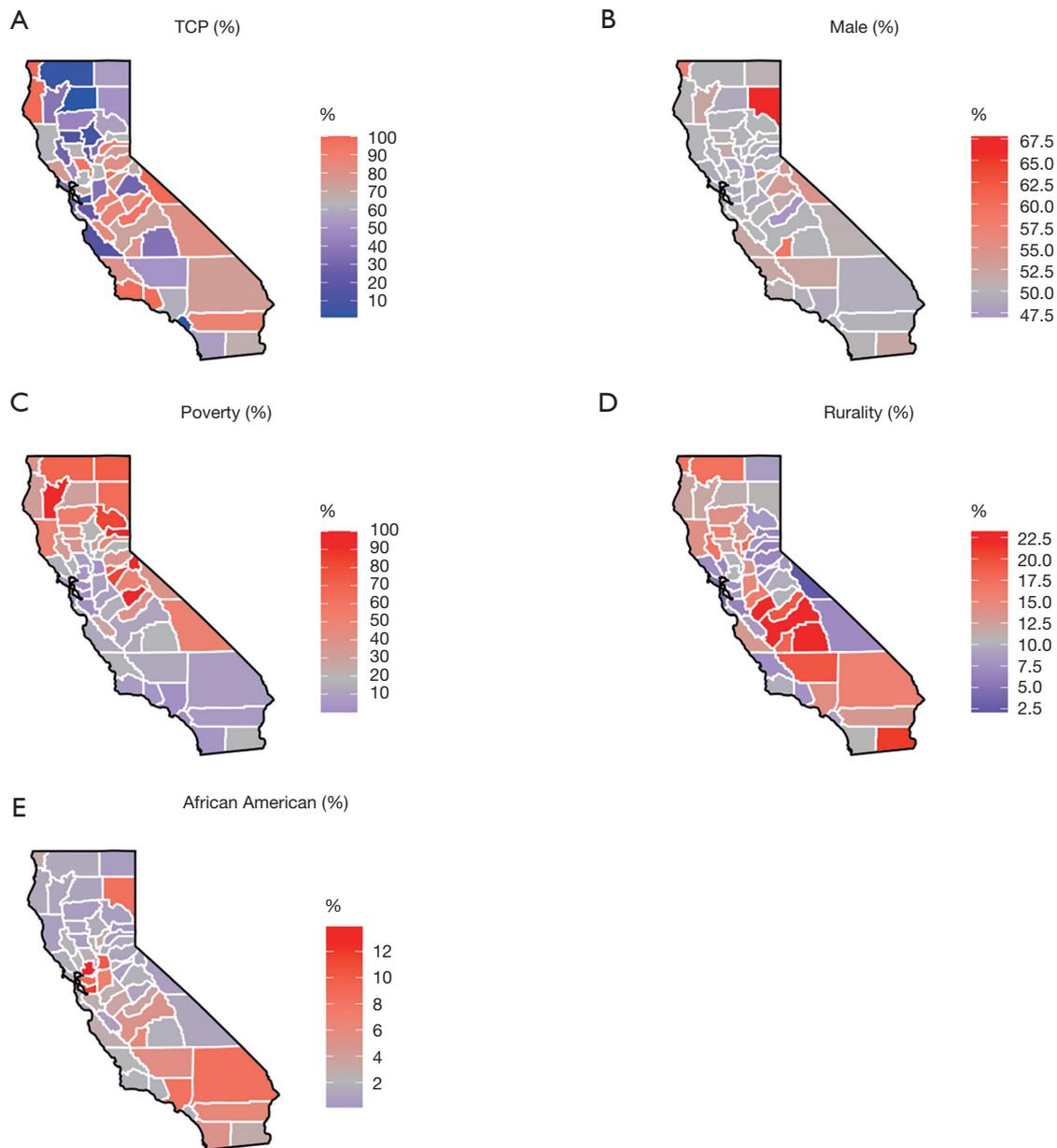
Figure 1 Maps of % TCP by area characteristics (orange: above median; grey: around median; purple: below median). TCP, trichloropropane.

random effect. The remaining models were based on the spatial model with different random effects and covariates, either with or without geographically weighted regression (GWR). For all models with random effects, there are no major qualitative differences between DIC and WAIC, suggesting that both measurements are appropriate for using when comparing models. Models 1(a) and 1(b), 2(a) and 2(b), 3(a) and 3(b), are models with no covariates.

Among all the models considered for stomach cancer, model 12(a) and model 13(a) are the two models have the lowest WAIC values. Due to the model complexity, we chose model 12(a) (percent below poverty level, percent of rural area, and percent of the allowed TCP, UH + CH effects, without GWR) as the best model. For the same reason, among all the models considered for liver cancer, model 10(b) (percent below poverty level, percent of rural
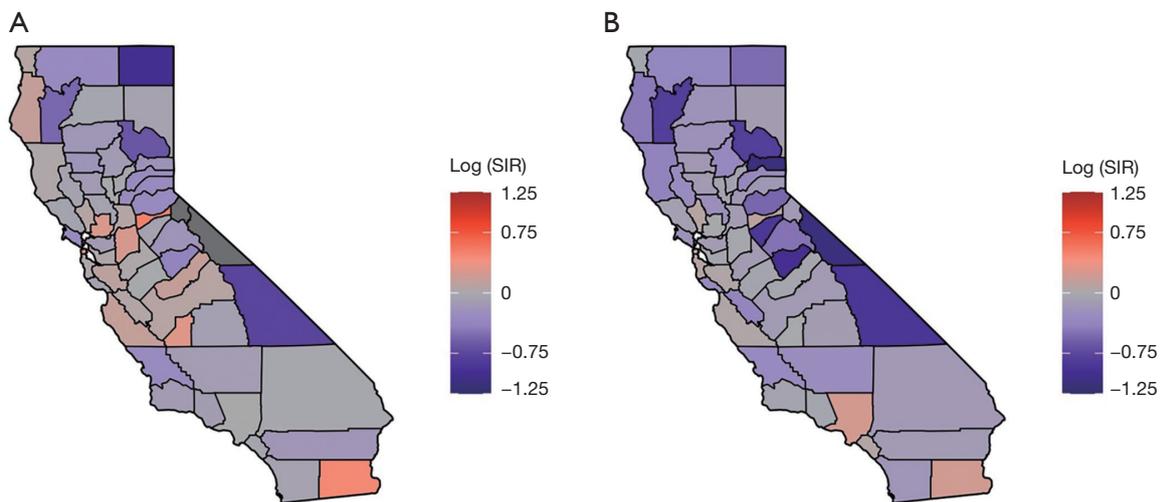
Figure 2 Maps of SIR in logarithm scale for stomach (A) and liver (B) cancers (color in orange: above 0; color in grey: around 0; color in purple: below 0; color in deep grey: no event as SIR =0). SIR, standardized incidence ratio.

Table 1 Model selection for the models considered (stomach cancer)

Model	Variables considered	Model names	WAIC	WpD	DIC	pD
Model 1 (a)	No covariates	No random effect	1,225.83	113.31	1,089.63	1.12
Model 2 (a)	No covariates	UH	456.85	23.21	462.39	36.85
Model 3 (a)	No covariates	UH + CH	451.47	21.02	459.16	35.87
Model 4 (a)	All covariates	No random effect	901.9	101.79	778.7	6.091
Model 5 (a)	All covariates	UH	447.78	20.06	453.78	32.88
Model 6 (a)	All covariates	UH+GWR	457.66	22.29	460.7	32.75
Model 7 (a)	All covariates	UH + CH	447.63	19.47	452.18	30.52
Model 8 (a)	All covariates	UH + CH + GWR	454.38	31.92	448.518	19.56
Model 9 (a)	Poverty (%) + rural (%) + TCP (%)	No random effect	905.82	92.52	793.05	4.102
Model 10 (a)	Poverty (%) + rural (%) + TCP (%)	UH	448.43	20.11	453.82	32.28
Model 11 (a)	Poverty (%) + rural (%) + TCP (%)	UH + GWR	449.7	20.4	455.51	33.1
Model 12 (a)	Poverty (%) + rural (%) + TCP (%)	UH + CH	445.96	19.26	452.99	32.75
Model 13 (a)	Poverty (%) + rural (%) +TCP (%)	UH + CH + GWR	445.64	19.16	454	33.93

All covariates include 1,2,3-trichloropropane (TCP) in drinking water (%), poverty in percent (%), rurality (%), gender (%), and race (%). UH, uncorrelated random effects; CH, spatially correlated random effects; GWR, geographically weighted regression.

area, percent of the allowed TCP, UH effect only, without GWR) was selected. For the models selected, model 12(a) for stomach cancer and model 10(b) for liver cancer, the DIC and WAICs are both smaller than model 2(a) and (b), and model 3(a) and (b), which are the models without covariates, but with UH or UH+CH random effects.

Tables 3,4 include the posterior results for the parameter estimates of model 12(a) and model 10(b). For both stomach and liver cancers, the percent of rural area and percent below poverty level were significant determinants. Specifically, according to model 12(a), one unit increase of the percent of poverty increased the relative risk of

Table 2 Model selection for the models considered (liver cancer)

Model	Variables considered	Model name	WAIC	WpD	DIC	pD
Model 1 (b)	No covariates	No random effect	1,283.44	28.42	1,254.95	1.16
Model 2 (b)	No covariates	UH	490.49	25.71	499.53	43.81
Model 3 (b)	No covariates	UH + CH	490.15	25.13	499.32	43.08
Model 4 (b)	All covariates	No random effect	1,257.47	138.87	1,097.58	6.13
Model 5 (b)	All covariates	UH	487.13	24.92	496.78	43.35
Model 6 (b)	All covariates	UH + GWR	488.8	26.09	495.67	42.12
Model 7 (b)	All covariates	UH + CH	492.98	25.47	497.31	38.53
Model 8 (b)	All covariates	UH + CH + GWR	491.22	24.97	497.53	39.9
Model 9 (b)	Poverty (%) + rural (%) + TCP (%)	No random effect	1,354.14	125.87	1,213.09	4.14
Model 10 (b)	Poverty (%) + rural (%) + TCP (%)	UH	486.45	24.8	496.18	43.28
Model 11 (b)	Poverty (%) + rural (%) + TCP (%)	UH + GWR	488.46	26.13	495.38	42.28
Model 12 (b)	Poverty (%) + rural (%) + TCP (%)	UH + CH	488.35	24.84	495.92	41.06
Model 13 (b)	Poverty (%) + rural (%) + TCP (%)	UH + CH + GWR	487.56	24.59	496.28	41.9

All covariates include 1,2,3-trichloropropane (TCP) in drinking water (%), poverty in percent (%), rurality (%), gender (%), and race (%). UH, uncorrelated random effects; CH, spatially correlated random effects; GWR, geographically weighted regression.

Table 3 Coefficient estimates of the selected best model for stomach cancer [Model 12 (a)]

Variables	UH + CH model	
	Mean (std dev)	95% CI
Intercept	0.808 (0.058)	0.697–0.926*
Poverty (%)	1.013 (0.004)	1.004–1.021*
Rural (%)	0.995 (0.001)	0.993–0.998*
TCP (%)	0.984 (0.070)	0.854–1.129

*, indicates that 1 does not belong to the 95% CI.

Table 4 Coefficient estimates of the selected best model for liver cancer [Model 10 (b)]

Variables	UH model	
	Mean (std dev)	95% CI
Intercept	0.806 (0.075)	0.664–0.961*
Poverty (%)	1.015 (0.006)	1.004–1.026*
Rural (%)	0.998 (0.001)	0.995–0.999*
TCP (%)	1.108 (0.102)	0.921–1.319

*, indicates that 1 does not belong to the 95% CI.

stomach cancer by 1.3% (95% CI: 0.4–2.1%); one unit increase of the percent of rural area decreased the relative risk of stomach cancer by 0.5% (95% CI: 0.2–0.7%). And, according to model 10(b), one unit increase of the percent of poverty increased the relative risk of stomach cancer by 1.5% (95% CI: 0.4–2.6%); one unit increase of the percent of rural area decreased the relative risk of stomach cancer by 0.2% (95% CI: 0.1–0.5%). However, we did not find any association between percent of the allowed TCP for either cancer type.

Figure 3A displays the log relative risk (uncorrelated and spatially correlated heterogeneity (UH + CH) random effects) estimated in model 12(a), and *Figure 3B* includes the log relative risk [the uncorrelated heterogeneity (UH) random effects] estimated in model 10(b). Both maps present a variability of the distribution of stomach and liver cancers in California. The map of liver cancer shows a higher variability when compared with the map of stomach cancer. For stomach cancer, the estimated log relative risk was between –0.13 and 0.27. Among them, 24 out of 58 counties had a log relative risk greater than 0. For liver cancer, the estimated log relative risk ranged between –0.27 and 0.60. Among them, 29 out of 58 counties had a log
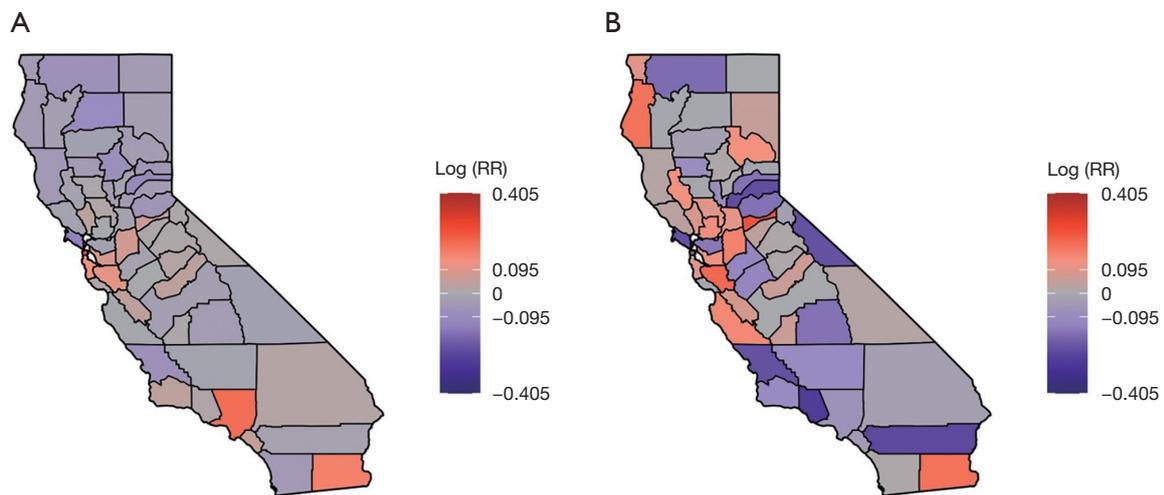
Figure 3 Maps of random effects [estimated log(RR)] for model 12 (A) and model 10 (B) (color in orange: above 0; color in grey: around 0; color in purple: below 0).
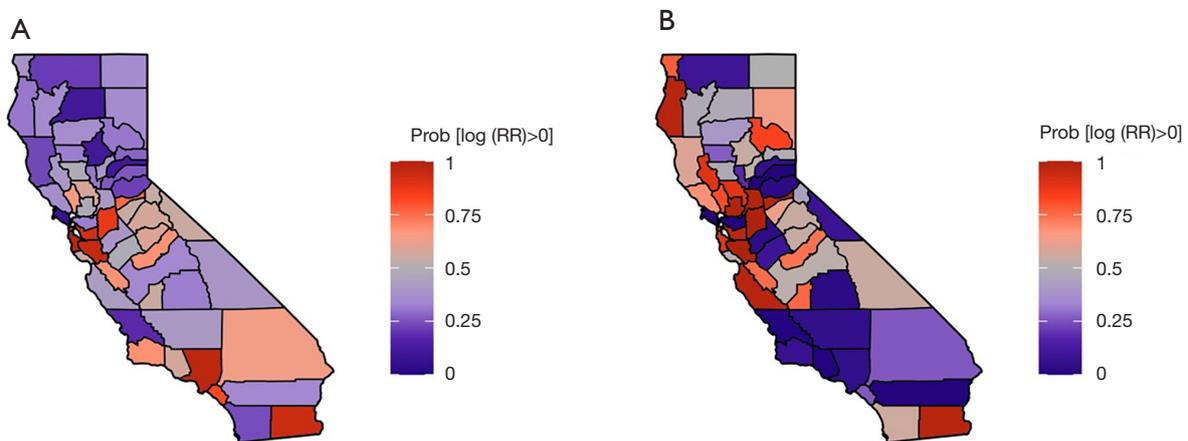
Figure 4 Maps of probably of random effects >0 [estimated log(RR) >0], model 12 (A) and model 10 (B) (color in orange: probability above 0.5; color in grey: probability around 0.5; color in purple: probability below 0.5).

relative risk greater than 0. *Figure 4A,4B* provides the map of probability of log RR greater than 0 estimated by model 12(a), and the map of the probability that the estimated log(RR) >0 estimated by model 10(b). The orange, grey, and purple colors visualize these probabilities in categories of greater than 0.5, around 0.5, and less than 0.5. For stomach cancer, a small cluster of excess risk was located in the mid-west region. For liver cancer, the counties with higher liver cancer relative risk were clustered from the mid-west (Bay area) to northwestern region. In addition, for both stomach and liver cancers, the excess risk was also found in Imperial county located in the southmost county.

Discussion

In our spatial Bayesian analysis, models with random effects greatly outperformed the models without random effects. There was a marked spatial variation of liver cancers in California at the county level. Also, we have found lower risk for each cancer type associated with rural regions, and an increased risk associated with poverty. Our findings agree with the results from other studies. For example, in 2003, Horton discussed the socioeconomic factors, including poverty and rurality with cancers, such as stomach and liver cancers (31). He concluded that less developed societies

tend to have higher cancer incidence. Also, Kogevinas *et al.* in 1997 pointed out that in the lower social strata, excess risks were found in both stomach and liver cancers (32). In other studies, both cancers were found to be more common in males than in females (3,33). Also, among other races and ethnicities, the two cancers were found to be the least prevalent among non-Hispanic Whites (3,33). However, we have not found any association related to sex and ethnicities.

Limitations of our project includes the fact that the data used for TCP were not a random sample and instead based on the available tests during the time periods considered. The TCP data were collected based on the regular monitoring of drinking water chemicals by California water boards. Each community water system is required to collect four quarterly samples during the designated year prior to any treatment. The designated year is based on historical monitoring frequency and laboratory capacity by the state water board (34). Also, the presence of TCP above the allowed level does not necessarily mean the water was used as drinking water. Both the continuous TCP data and percent of the allowed TCP were considered, but no association result was found. Also, due to confidentiality, individual data was not available, and the data was aggregated at the county level. As a shortfall of ecological study, there is a loss of information due to aggregation. Therefore, further studies should examine the reasons for the association between poverty and rurality between stomach and liver cancers. A limitation in the modeling is that instead of age adjusted expected incidence, general expected incidence was used.

Our findings could help public health officials identify regions with higher cancer relative risk, and better understand the risk factors for these diseases, such as spatial location, poverty and rurality. This can help public health administrators more appropriately plan and target the use of available resources to reduce the burden in the high risk areas. Suggestions include motivating screening for established risk factors and prevention activities and increasing the public awareness of stomach and liver cancers in high risk areas.

Acknowledgments

Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/ace-19-21). The series "Spatial Patterns in Cancer Epidemiology" was commissioned by the editorial office without any funding or sponsorship. The authors report that this work was funded by the college of Art and Science, Western Michigan University. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The project does not include human subject research since we used aggregated data at the county level. No ethnics approval is required.

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