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Original

Bayesian Spatial analysis for breast and prostate cancer incidence in Sudan based on 2009-2013 national registry data.

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Abstract

Background: The spread of cancer disease has been a problem and burden on the global health systems what led the decision makers and researchers to encourage further investigations research on related issues. In Sudan, research there is still a need to work on advanced applications such as Bayesian models or relative risk estimations based on Bayesian methods. **Materials & Methods**: This paper investigates the spatial impact on the incidence of cancer in Sudan using Bayesian and Frequentist methods. The standardized incidence ratios have been calculated for each state, and INLA with BYM have been used in the investigation. Disease mapping is useful to determine which areas are with high-risk rates what can be conducted under the Latent Gaussian Model. R-INLA package has been used as tool of modeling. Data collected by National Cancer Registry through 2009-2013, handed to the researcher on 2016, actually, it is the only available complete data in Sudan at the present time, while the population data for the same period is estimated by the Central Bureau of Statistics (CBS). For the period 2009-2013, a number of 45413 cancer patients were recorded throughout Sudan, among all cases registered, Breast cancer count was5892Cases, and Prostate was 2315. Females were 24,439, 54% among the whole cases while males 20,974, 46%. For all cancer cases including gender specific cancers, females appeared to have the highest number of incidences compared to males. **Results:** Results from this study- in two parts- revealed that, the standardized incidence rates indicate the wide spread of the cancers under study in Northern state and River Nile state; the spatial Bayesian analysis using INLA indicates results similar to standardized incidence rate. **In conclusion**, the Northern and River Nile were the most affected states in Sudan with breast and prostate cancers requiring further studies in identifying what factors causes the problem. The general trend of the study indicated widespread breast and prostate cancer in Northern state and River Nile state.
Keywords: INLA, LGMs, Cancer, Sudan, Spatial analysis, Relative Risk. Incidence rate

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Introduction

The wide spread of cancer is a problem of global concern, [1] [2] affecting the human and communities' development [3]. The literature on cancer nowadays is growing fast to cover all multidisciplinary areas and advanced statistical modeling techniques, e.g., based on Bayesian principles, have proven high levels of reliability and flexibility in the latest decades. However, thorough analyses of cancer incidence in African countries are still missing. The present study investigates the spatial impact of cancer incidence in Sudan based the available data from the national registry center, covering the period 2009-2013 for the whole country.

Research on cancer incidence in Sudan is sparse. Using the Box-Jenkins method as time series tool [4], 2013 have shown that cancer incidence in Sudan is continuously increasing. A spatial analysis of breast cancer only in Sudan during 2010-2016 has been conducted [5] based on 4423 cancer cases, analyzed using SPSS and mapped using ArcGIS. It revealed that, the areas that marked higher risk rates are: Nile River, Northern, Red Sea, North and South Kordofan and White Nile. A population-based [2] study in 2018 investigating 45413 cancer cases during the years 2009-2013 shows that in Sudan males are significantly more susceptible to cancers in 80% of the top 35 cancers when excluding sex-specific cancers. In 2012 it is mapped the incidence of cancer in Sudan using GIS [6]. However, no advanced modeling techniques have been applied for Sudan cancer incidence data for investigating the effects of different regions on cancer incidence. To this end, this study aims to perform Bayesian (including Integrated Nested Laplace Approximation, INLA) along with Frequentist's methods based on Poisson regression. to investigate the spatial impact on cancer incidence in Sudan based on data from 2009 to 2013.

Bayesian models which are simulation-based technique were working previously under Markov Chain Monte Carlo (MCMC). Recently, the Integrated Nested Laplace Approximation (INLA), has risen as anapproximation-based method, proved flexibility and usefulness in handling the Bayesian applications of the latent Gaussian models (LGMs) providing an approximation for hyper parameters of the posterior marginal of the latent variables. The posterior marginal of latent Gaussian models described as: $\pi(x_i|y) = \int_{\theta} \pi(x_i|\theta, y)\, \pi(\theta|y)\, d\theta$. Moreover, it covers space-time applications [7], disease mapping [8],[9], generalized linear models, generalized Linear Mixed

Models [10], Log-Gaussian Cox process [11], survival models [12], and in more details the Spatial Bayesian monograph [13]. INLA has been frequently used for disease mapping [8], smoothing covariates within spatial and Spatio-temporal models [14] based on Besag York and Mollie (BYM) modeling technique [8], [13], [15].

To spatially model the log-relative risk of cancer, all fixed and random effects should be investigated. Models are applicable jointly under fully Bayesian (INLA) and Besag, York, and Mollie (BYM) method. Historically, the spread of Bayesian applications in epidemiology and Biostatistics is mainly due to the revolution in computational facilities, especially R platform.

The R is rich with hundreds of packages that serve in different disciplines including medical sciences. The package R-INLA, handles the latent Gaussian models was introduced by Rue, Martino and Chopin in 2009 [16].

Data description: (Are there caveats?)

Data for research collected, purified and classified by the National Cancer Registry Center (NCR).The data feed is from different sources of data such as hospitals, laboratories, death certificate, and the registry centers. The Radiation and Isotope Center, Khartoum (RICK) and the Institute of Nuclear Medicine, Molecular Biology and Oncology (INMO) are providing more than 80% of the available data in Sudan [17] . A minor part of cancer data was taken from National Health laboratory (ESTAC), the referral governmental laboratory in Sudan due to its activity in histopathology. The main platform for cancer data registrationis CanReg5 as the data are available mostly from hospitals and laboratories for registry personnel through scheduled visits. According to CanReg5; the targeted type of data includes patient's identification, demographic information, site of cancer, (topography), histology (morphology), stage, behavior, extent of the disease and basis of diagnosis.

At the time of data collection, 2012, there were only 16 states in Sudan. The states were; Khartoum, North Kordofan, Northern State, Kasala, Blue Nile, South Kordofan, Algazira, White Nile, River Nile, Red Sea, Gadarif, Sinnar, West Kordofan, North Darfor, West Darfor, Central Darfor, South Darfor, East Darfor was added later as part of the map.

The following graph shows the administrative difference between the western states before and after 2012. (Administrative changes)

Figure1, States Before 2012 States after 2012

Figure1, states of Sudan before 2012

The estimated population for the year 2013 is 36163778, 18433476 of them are males and 17730302 are females. The data was taken officially from the Central Bureau of Statistics (CBS), Sudan. Among all cases registered, Breast cancer is the most incident (7497 Cases, 16.5%), followed by Leukemia (3932, 8.7%), Prostate (3002, 6.6%), Lymphoma (2908, 6.4%), and Esophageal cancer (2203, 4.9). Females were 24,439, 54% among the whole cases while males 20,974, 46%.

With 7497 (16.5%) cases, the breast cancer placed first among the most incident cancer in Sudan for the period, followed by Leukemia 3932 (8.7%). The following graph shows the most incident 20 cancers in Sudan for study's period:

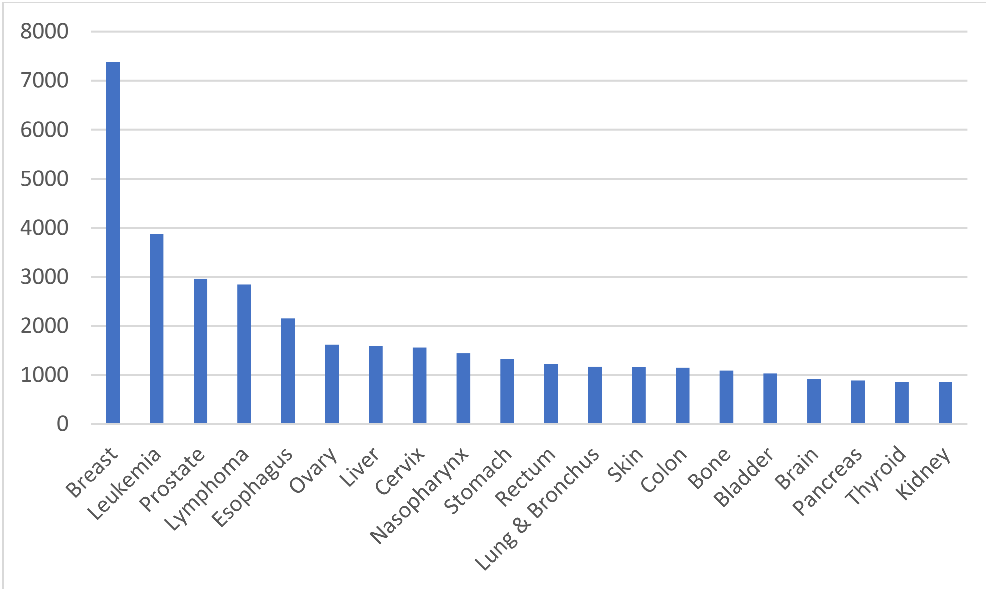

Figure2. the 20 most incident cancers in Sudan

The article includes an abstract which summarizes the findings of the research. The introduction to the research problem, the techniques used in the study and the weight of the work. Next section illustrates the methods being used in the research work including standardized Incidence Ratio (SIR), Generalized Linear Models (GLMs), Bayesian Models, and Latent Gaussian Models (LGM).results and analysis are provided. Finally, the conclusion relates the study to the situation of cancer incidence in Sudan from Bayesian point of view. Lastly, the references illustrate the source of literature that used in the article.

Methods

In this section a description is given for the generalized linear models (GLM) as it is used for Disease Mapping and the Integrated Nested Laplace Approximation as approximation method for inference for the Bayesian GLM

The standardized Incidence Ratio (SIR)

The incidence rate measures the occurrence of new cancer cases within a specified time. While the Standardized Incidence Ratio (SIR) is used to determine if the occurrence of cancer in a relatively small population is high or low. SIR analysis tells if the number of observed cancer in a particular geographic area is higher or lower than expected, given the population and age distribution for that community. The SIR can be calculated by dividing the observed number of cases of cancer by the “expected” number of cases. To compute standardized incidence ratio, the expected number of cases $e_i = n_i * \frac{Y}{N}$ where

$n_i$is the number of people under risk in area I, N is the number of people in all areas and Y is the number of cases in all areas, after that e_i will be multiplied with the count in each area y_i.

The Generalized Linear Models (GLMs)

The generalized linear models (GLMs) is a regression technique usedif normality of responses violated, i.e., it handles the regression where response variable follows any member of the exponential family e.g. Gaussian, Binomial, Poisson, and Gamma distribution. The GLMs model consists of:

- The independent responses $Y: (Y_1, \dots, Y_n)$, and its associated distribution's function, which should be member of the exponential family, linear predictor of a GLMs.
- The linear predictor $\eta = X\beta$connects the predictors to η which is related to E(Y).
- The link function connects the linear predictors to the random component. (AGRESTI, 2015)

$$g(\mu_i) = \sum_{j=1}^{p} \beta_j x_{ij}, i = 1,2, \dots, n$$

The mathematical formula is$\mathrm{E(Y_i)} = (\mathrm{COUNT}) = \beta_0(Intercept) + \beta_1(\mathrm{STATE})$.Its code under R is as follow: glm(COUNT ~ STATE, family=poisson, data=data), Null deviances and residual deviances were used to distinguish between different models.

Bayesian Models

The Poisson distribution with probability function $P(X = x) = \frac{e^{-\lambda}\lambda^y}{y!}; y = 0,1,2, \dots,$ E[y] = λ (The expectednumber of events) and V[y] = λ. Where the link function is $\eta = \log(\lambda_i) = x_i\beta$, so $\lambda_i = \exp(x,\beta)$; $\lambda >$ 0.While the Poisson regression is featured with the log link called a log-linear model as follow$\log(\mu) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k$

The methods of Poisson regression handle the expected value asa function of regional covariates:$log\{E(Y_i)\} = X\beta$, $E(Y_i) = exp(X\beta)$. The number of cases (y_i) in area i are following Poisson distribution with mean$e_i\theta_i$, y_i~ Poisson ($e_i\theta_i$), where $e_i$is the expected number of cases in the ith geographic area, and θ_i is the relative risk in area$i$. The log-relative risk rate is suitable and expressive for disease mapping. Taking the following formula: $y_i \sim Poisson\left(E_i exp(\eta_i)\right)$, Where the;$\eta_i = \mu + u_i + v_i + f(c_i)$ is a log-relative risk rate.

- μ; is the intercept and the average rate for all regions.
- u_i; is a structured spatial component

- v_i; is unstructured component
- $f(c_i)$; is the nonlinear effect of the covariate c.

Latent Gaussian Models (LGM)

The Latent Gaussian models (LGM) considered additive regression model consist of Likelihood model $\pi(y|x,\theta) = \prod_{i=1}^{n} \pi(y|\eta_i(x),\theta)$, Where $y = (y_1, \dots, y_{nd})^T$ is the response vector $x = (x_1, \dots, x_n)^T$; The latent field, and $\theta = (\theta_1, \dots, \theta_m)^T$, The hyper parameters vector $\eta_i(x)$ and the i^th^ linear predictor connects data to the latent field.

Latent Gaussian field $x|\theta \sim N(\mu(\theta), Q^{-1}(\theta))$, where Gaussian distribution attributed with mean $\mu(\theta)$ and precision matrix $Q(\theta)$ to the latent field x conditioned on thehyperparameter θ.

Hyper parameters $\theta \sim \pi(\theta)$, assigns prior distribution to the hyperparameters

LGMs are flexible enough to handle the spatial and spatiotemporal models [18]. The spatial epidemiology focuses on estimating risk rates related to parameters or investigating the autocorrelation between the different regions, determination the random effects that encompass the structured and unstructured heterogeneity of covariates. Under INLA, the formula in R can be described as follow: inla(COUNT~STATE, family = "poisson", data = data, control. compute=list(dic=FALSE))

Results and discussion

During 2009 – 2013, as a result of a detailed work done by the national cancer registry in Sudan, a number of 45411 cancer cases have been recorded. From the initial view, among 117 types of cancers in Sudan, Breast, and Prostate were at the top with statistics 5892, and2315 respectively. The following tables show, for breast and prostate cancer, the standardized incidence rate (SIR), the covariates for all states estimated by glm and INLA.

Table1, Breast Cancer analysis

STATE	Male			Female			Male		Female	
	Count	Population	SIR	Count	Population	SIR	GLM (β)	INLA(mean)	GLM (β)	INLA(mean)
Khartoum	70	3466307	1.373627	1822	3068488	1.872951	0.6376	0.638	0.70530	0.705
Algazira	37	2065810	1.218286	900	2219598	1.279001	2.2246	2.224	5.41610	5.416
South Darfor	13	2455227	0.360155	156	2246065	0.219081	-1.0460	-1.046	-1.75254	-1.752
North Kordofan	30	1107468	1.842587	425	1195030	1.121793	-0.2097	-0.209	-0.75031	-0.750
North Darfor	12	1137540	0.717551	159	1093765	0.458538	-1.1260	-1.126	-1.73349	-1.733
Kasala	14	1178401	0.808114	170	955262	0.561344	-0.9719	-0.972	-1.66660	-1.667
White Nile	21	1022735	1.396671	354	1063915	1.04954	-0.5664	-0.566	-0.93310	-0.933
Gadarif	7	863584	0.551355	141	875894	0.507774	-1.6650	-1.665	-1.85363	-1.854
West Kordofan	4	788517	0.345054	30	810061	0.116817	-2.2246	-2.224	-3.40120	-3.401
Sinnar	4	769200	0.353719	201	811157	0.781616	-2.2246	-2.224	-1.49909	-1.499
Red Sea	4	780424	0.348632	145	586567	0.779746	-2.2246	-2.224	-1.82566	-1.826
River Nile	21	667901	2.138677	495	641228	2.434979	-0.5664	-0.566	-0.59784	-0.598
South Kordofan	8	485687	1.120396	115	498962	0.726997	-1.5315	-1.531	-2.05746	-2.057
Blue Nile	4	489036	0.556362	48	476537	0.317722	-2.2246	-2.224	-2.93119	-2.931
West Darfor	6	743963	0.548577	72	785764	0.28903	-1.8192	-1.819	-2.52573	-2.526
Northern State	16	411676	2.64364	388	402009	3.044377	-0.8383	-0.838	-0.84139	-0.841

Table2, Prostate Cancer analysis

STATE	Male			Female			Male		Female	
	Count	Population	SIR	Count	Population	SIR	GLM (β)	INLA (mean)	GLM (β)	INLA (mean)
Khartoum	741	3466307	1.704396	1	3068488	1.872951	0.73588	0.736	2.609e-15	0.996
Algazira	355	2065810	1.370116	1	2219598	1.279001	4.48582	4.486	-1.386e+00	-2.389
South Darfor	85	2455227	0.276024	0	2246065	0.219081	-1.42947	-1.429	-2.092e+01	-4.480
North Kordofan	159	1107468	1.144683	0	1195030	1.121793	-0.80321	-0.803	-2.092e+01	-4.480
North Darfor	89	1137540	0.623796	0	1093765	0.458538	-1.38348	-1.383	-2.092e+01	-4.480
Kasala	50	1178401	0.338296	0	955262	0.561344	-1.96009	-1.960	-2.092e+01	-4.480
White Nile	137	1022735	1.068014	0	1063915	1.04954	-0.95214	-0.952	-2.092e+01	-4.480
Gadarif	77	863584	0.710895	1	875894	0.507774	-1.52831	-1.528	1.636e-15	0.996
West Kordofan	22	788517	0.222449	0	810061	0.116817	-2.78108	-2.781	-2.092e+01	-4.480
Sinnar	92	769200	0.953604	0	811157	0.781616	-1.35033	-1.350	-2.092e+01	-4.480
Red Sea	28	780424	0.286053	0	586567	0.779746	-2.53991	-2.540	-2.092e+01	-4.480
River Nile	170	667901	2.029347	0	641228	2.434979	-0.73632	-0.736	-2.092e+01	-4.480
South Kordofan	90	485687	1.477425	0	498962	0.726997	-1.37231	-1.372	-2.092e+01	-4.480
Blue Nile	22	489036	0.358675	0	476537	0.317722	-2.78108	-2.781	-2.092e+01	-4.480
West Darfor	32	743963	0.34294	0	785764	0.28903	-2.40638	-2.406	-2.092e+01	-4.480
Northern State	163	411676	3.156832	0	402009	3.044377	-0.77837	-0.778	-2.092e+01	-4.480

Regarding the comparison between Glm and R-INLA, both of them produce the log value because of link functions in the models, so th e exponential values of the estimates or of th e approximated parameters is important. Acc ording to the Null deviances 400.65 and Resi dual deviances 197.12, the model is represen tative. One more graph base on fitted values and residual value is supportive. For female, the Null deviance and residual deviance sho ws significant impact upon the COUNT vari able.

Male Female

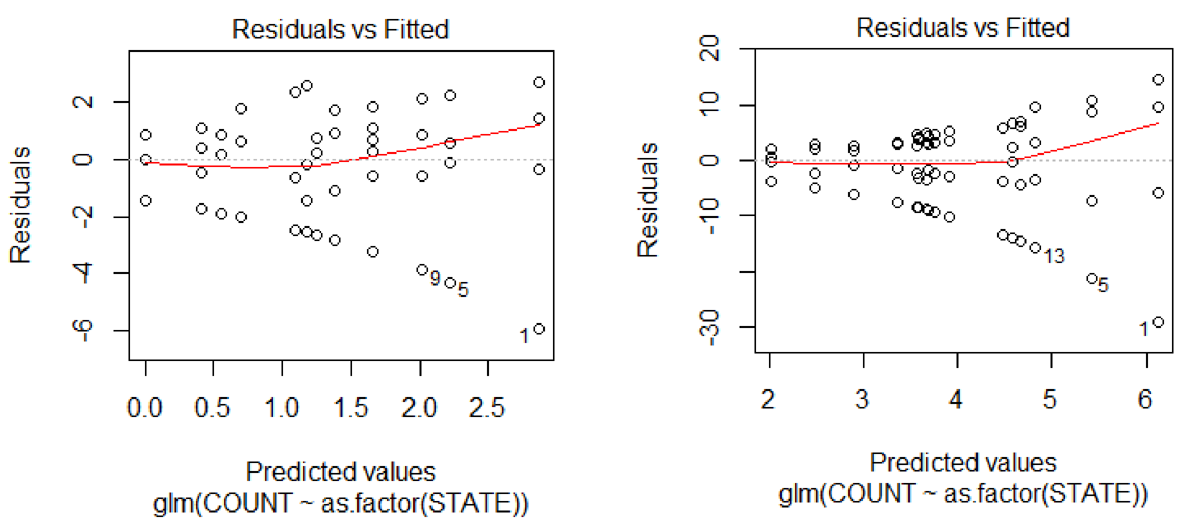

Figure3. Residuals vs. Fitted graph for Male and Female Breast Cancer Patients

These graphs for breast cancer show how model is representative even if sample is big.

Male Female

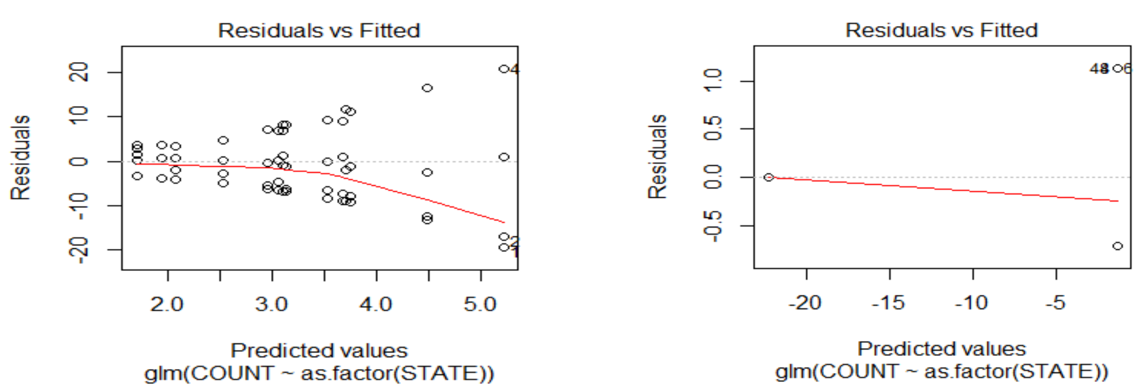

Figure4. Residuals vs. Fitted graph for Male and Female Prostate Cancer Patients

Prostate cancer rarely occurs among females, so the focus will be on males. For males, adding the state factor to the model changing the deviance from 5812.9 to 3543.6

From the results, cancer incidence in Sudan for the period 2009-2013 have been investigated spatially to pave the way for further studies, to include suspected risk factors.

Incidence wise, the Northern state and the River Nile state, for both genders have recorded the highest incidence rates. During the period, 5892 and 2315 breast and prostate cancer cases recorded. The Novel method, INLA have been used alongside with classic GLM to model the relationship between locations in Sudan and the number of cases. GLM represented the classical frequentist method of modeling and INLA as previously mentioned, represented the Bayesian part of the models based on the same factors, thus revealing the similarity of both methods based on estimation of covariates. Moreover, the tables show the standardized incidence rates, Exponential of beta for GLM, and the beta estimates using INLA.

Male **Female**

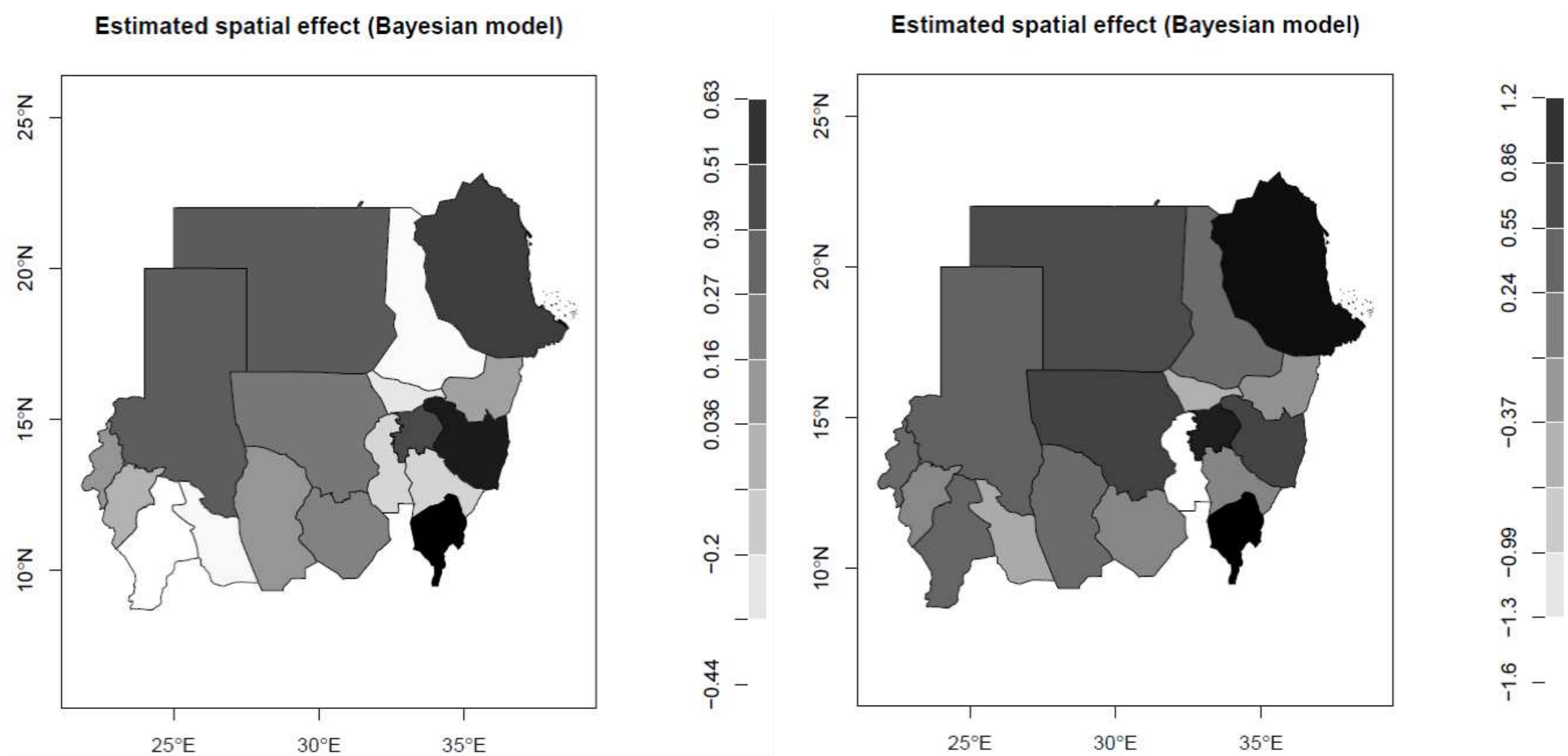

Figure5. INLA mapping for relative risk estimates for Breast cancer incidence in Sudan

Male **Female**

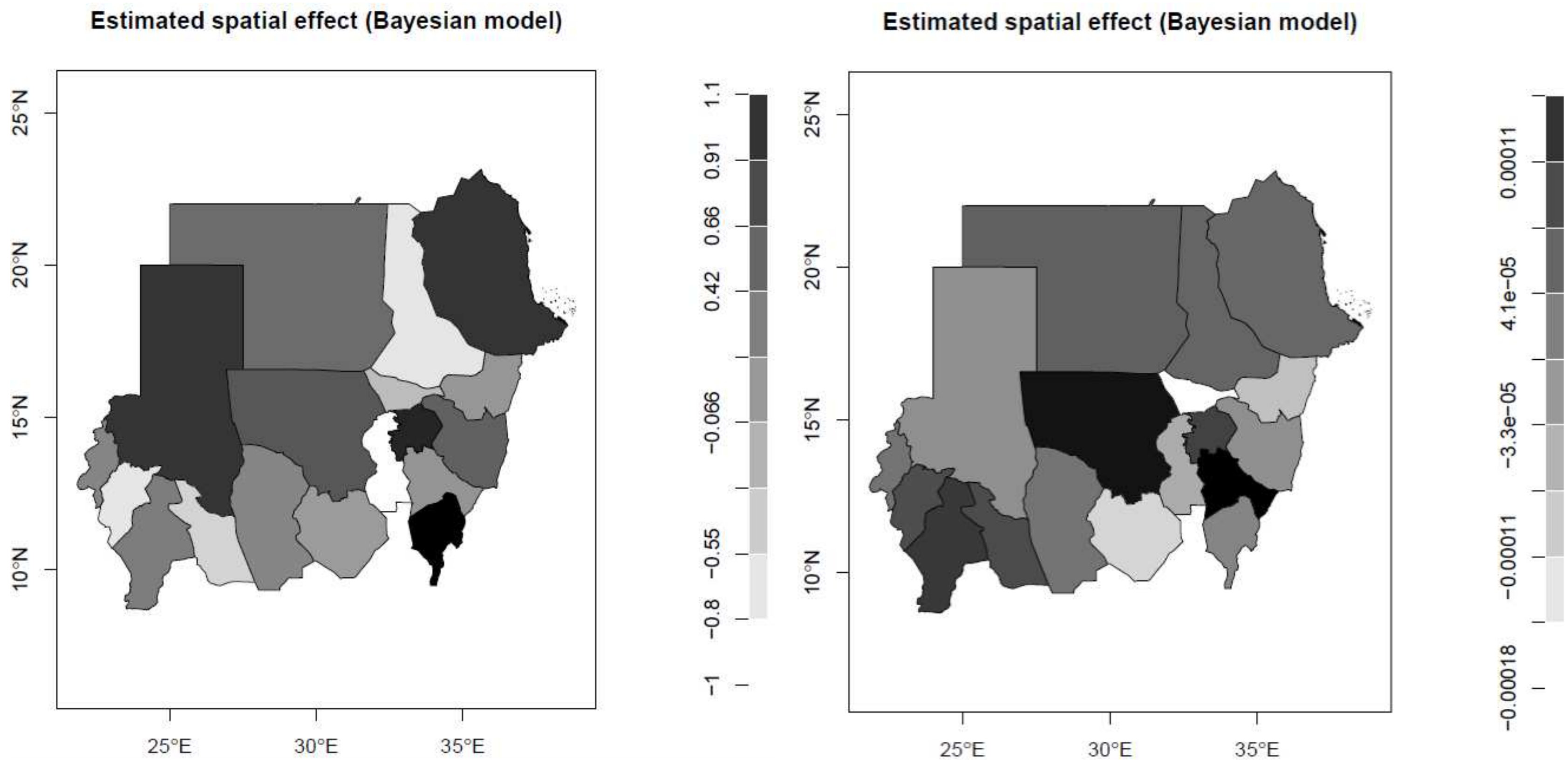

Figure 6. INLA mapping for relative risk estimates for Prostate cancer incidence in Sudan

The following map shows the log-relative risk of breast cancer incidence in Sudan during 2009-2013 which approximated using R-INLA. Shadows represent log-relative risk rates approximated using R-INLA, so it is approximated as Bayesian spatial impacts of the states in Sudan.

The map's legend refers to the log relative risk in a region. The relative risk value after exponentiation if greater than one, it indicates higher risk compared to standard population.

Some variation is clear if tables and maps were compared, which could be due to the smoothness of relative risk estimates depending on age. The smoothed relative risk estimates take their values come mostly from neighboring states.

For prostate cancer, only males will give the right results of Bayesian modeling. Males' relative risk estimates in this table are consistent with SIR values in table 6.

It is useful to compare the relative risk rates to investigate the cancer incidence between two or more groups. A relative risk of value one indicates the absence of variations in risk rates between the state and the intercept. The relative risk of greater than1 indicates: the risk of developing disease is higher comparing intercept and vice versa.

Disease mapping and ecological regression modeling are important techniques when handling the epidemiological spatial studies, especially the studies with the aggregated data. The spatial analysis is useful for identifying the dependence neighboring regions. Besag-York-Mollie (BYM) models are connecting the disease mapping, relative risk estimation and spatial analyses as appears widely in recent research works. The Integrated Nested Laplace Approximation (INLA) which based on the well-known Latent Gaussian Models (LGMs) has proven reliability for spatial analysis.

The general trend of the study except the maps, revealed the wide spread of cancer in Northern state and River Nile state in most types of cancers investigated starting with standardized incidence rates and classical Poisson regression as generalized linear models followed by Bayesian Poisson regression and finally spatial Bayesian modeling using INLA and BYM. Regarding the established maps, the coded is well designed and revised many times, meticulously, maps are not consistent with all results here, but anyhow, there many reasons that could justify that. primarily, the technique used here is relying on smoothed relative risk estimates which take their values from neighboring states. One more reason is that the variation in this, study is based on modified shape file as the current shape wouldn't work due federal restructuring in Sudan before the time of data collection.

Conclusion

During 2009-2013, a number of 45413 cancer patients were recorded throughout Sudan. Among all cases registered, Breast cancer is the most incident (7497 Cases, 16.5%), higher than Prostate cancer incidence (3002, 6.6%). Females were 24,439, 54% among the whole cases while males 20,974, 46%. For all cancer cases including gender specific cancers, females appeared to have the highest number of incidences compared to males. significently be mentioned here, the locations of the biggest oncology hospitals are Khartoum and Algazira states while the actual priority should be given to the states with highest incidence rates i.e. Northern state and River Nile state.

The Poisson regression modeling has been used to investigate the relationship between the spatial factor and cancer incidence in Sudan what identified how cancer incidence differ from state to state in Sudan. According to null deviances and residual deviances computed from the models, the models for breast and prostate cancers per genders was well established. Also, it is noted the similarity between results from regression models established by glm and regression models established by INLA, what indicates the quality of the models that established by both methods.

Also it appeared that, the applications of Bayesian spatial models using BYM and R-INLA are adequate for mapping breast and prostate cancers. Therefore, this part illustrated the application of Bayesian modeling on spatial aggregated cancer incidence data as latent Gaussian models. The well-known Integrated Nested Laplace Approximation (INLA) as tool of modeling and mapping used to map the log-relative risk rates for cancer incidence in Sudan. R-INLA package showed usefulness, flexibility and reliability in this area. The prostate cancer is a gender-specific cancer, common among males and rarely occur among female. Northern states and River Nile are suffering the highest incidence rates, the high counts that appeared in Khartoum were due to greater population.

The results obtained from this study can be divided into five main parts. Firstly, the standardized incidence rates revealed the wide spread of the cancers under study in Northern state and River Nile state. The second part of the study is the classical

Poisson regression under generalized linear models which revealed similar results to the third part of the results, the Bayesian Poisson regression, both results from classical and Bayesian Poisson regression are consistent and going alongside with the calculated standardized incidence rates. The fourth part of the results is spatial Bayesian analysis using the INLA method revealed results along the same lines bearing in mind the most affected state point of view. So these consistent results coincide reasonably well. Unlike, the maps which established based BYM and R-INLA package didn't coinde, but, as mentioned before, there are many reasons are expected to cause the variation.

In conclusion, the Northern state and River Nile states are the most affected states in Sudan with most sorts of cancers which requires further studies to identify factors causing such incidence.

Recommendations:

From the study, it is revealed that the following recommendations are important for cancer research in Sudan.

- Further studies are needed to identify the spatial factors behind the wide spread in these states.
- It is necessary to design an R package especial for Sudan's cancer data to be able to handle all important techniques such spatial Bayesian models.
- There appears to be a need to Establish new oncology hospitals in states with higher incidence rates, i.e., Northern and River Nile state.
- It is mandatory to continue in cancer registration data which represents the pillar of cancer research.
- It is important to publish the cancer data online for research purposes.

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