


RESEARCH ARTICLE

Estimating multilevel regional variation in excess mortality of cancer patients using integrated nested Laplace approximation

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Models of excess mortality with random effects were used to estimate regional variation in relative or net survival of cancer patients. Statistical inference for these models based on the Markov chain Monte Carlo (MCMC) methods is computationally intensive and, therefore, not feasible for routine analyses of cancer register data. This study assessed the performance of the integrated nested Laplace approximation (INLA) in monitoring regional variation in cancer survival. Poisson regression model of excess mortality including both spatially correlated and unstructured random effects was fitted to the data of patients diagnosed with ovarian and breast cancer in Finland during 1955–2014 with follow up from 1960 through 2014 by using the period approach with five-year calendar time windows. We estimated standard deviations associated with variation (i) between hospital districts and (ii) between municipalities within hospital districts. Posterior estimates based on the INLA approach were compared to those based on the MCMC simulation. The estimates of the variation parameters were similar between the two approaches. Variation within hospital districts dominated in the total variation between municipalities. In 2000–2014, the proportion of the average variation within hospital districts was 68% (95% posterior interval: 35%–93%) and 82% (60%–98%) out of the total variation in ovarian and breast cancer, respectively. In the estimation of regional variation, the INLA approach was accurate, fast, and easy to implement by using the R-INLA package.

KEYWORDS

cancer survival, excess mortality, integrated nested Laplace approximation (INLA), Markov chain Monte Carlo (MCMC), regional variation

1 | INTRODUCTION

Excess mortality of a patient diagnosed with a given disease is the additional hazard of death encountered by the patient compared to the hazard of death in a relevant reference population group. Monitoring excess mortality by region is important because variation in the excess mortality may reflect regional differences in the effectiveness of cancer care.¹ A comprehensive national health service system should ensure the same level of cancer care to all people in the country.

In Finland, inhabitants of a given municipality are most often treated in their own central hospital and further referred to the pertinent university hospital if more advanced hospital care is needed. Therefore, we are primarily interested in assessing regional variation across these central hospital districts or university hospital regions. However, equity across these hospital districts does not necessarily imply equity across municipalities within the districts.

The excess mortality can be summarized in terms of relative or net survival these quantities being often used in population-based cancer survival analyses to measure cancer survival after accounting for differences in reference population mortality.²⁻⁴ They have been used, eg, in the international comparisons of cancer survival between countries,^{5,6} between regions within a country,^{7,8} or between other population subgroups.⁹ The same methods apply to the assessments of mortality associated with diseases other than cancer, too, eg, cardiovascular^{10,11} and cerebrovascular diseases¹² and HIV.¹³

Excess mortality is often modeled by splitting follow-up time in prespecified intervals within which binomial distribution for the number of deaths¹⁴ or a piecewise constant excess hazard² is assumed. These models can be fitted in the framework of generalized linear models by using binomial or Poisson distribution with nonstandard link functions.¹⁵ When a piecewise constant excess hazard is assumed, there is a good argument for using shorter intervals early in the follow up, as patients' excess mortality often changes most rapidly in the beginning of follow up.¹⁵ Alternatively, baseline excess mortality has been parametrized by using mixture cure models¹⁶ and flexible parametric models.¹⁰ Modeling excess mortality with a nonparametric baseline excess hazard function has also been proposed.^{17,18}

The piecewise constant excess hazard model¹⁵ was extended by Kuss et al¹⁹ to account for clustered responses using spatially unstructured random effects. This model was fitted within the class of generalized linear mixed models by using maximum likelihood methods. In a Bayesian framework, a similar type of model with spatially correlated random effects has been used to assessing spatial variation in cancer survival by Fairley et al,²⁰ Cramb et al,²¹ Saez et al,²² and Kang et al.²³ Recently, Cramb et al²⁴ extended a flexible parametric model¹⁰ to estimation of spatial variation in excess mortality. The disadvantage of these Bayesian approaches is that they are computationally intensive²⁴ because the models are fitted by using Markov chain Monte Carlo (MCMC) methods.

In Bayesian inference, the integrated nested Laplace approximation (INLA) approach proposed by Rue et al²⁵⁻²⁷ is computationally more efficient than the MCMC methods. The INLA approach can be easily applied by using the R-INLA package²⁵ (www.r-inla.org) to a wide variety of statistical models including generalized linear mixed models. In the estimation of excess mortality and net survival, the INLA approach has been mentioned as a possible solution to overcome the computational challenges related to the MCMC approaches,^{23,24} but to our knowledge, it has not been employed for the estimation in practice.

In this paper, we apply the piecewise constant excess hazard model with spatially correlated random effects to the follow-up data of patients diagnosed with the cancers of ovary and breast in Finland. Variation in cancer survival is assessed in two levels, ie, across hospital districts and across municipalities within hospital districts. The model is implemented in a Bayesian framework using the INLA approach. The results are compared to those estimated by using the MCMC methods to validate the use of the INLA approach in the assessment of regional variation in excess mortality and net survival.

2 | EXCESS HAZARD MODEL WITH REGIONAL RANDOM EFFECTS

2.1 | Patients diagnosed with ovarian and breast cancer

We analyzed the follow-up data of women diagnosed with the cancers of ovary and breast (primary invasive malignancies with ICD-10 codes C56 and C50, respectively) in Finland and reported to the Finnish Cancer Registry. The patients were diagnosed in 1955-2014 and followed up for death in 1960-2014. In Finland, specialized hospital care is currently provided by 20 central hospital districts.²⁸ In addition, the autonomous region of Åland Islands was considered as a separate hospital district in the analysis. Each central hospital district consists of member municipalities and is subsumed under one of the five larger cancer control regions, each being lead by a university hospital. The analyses were based on the regional division of 313 municipalities that existed in Finland in 2016 (Supplementary Figure S1). Patient's municipality was based on her place of residence at the beginning of the year of diagnosis.

The period approach²⁹ was used in the analysis. The follow-up data were split into 11 five-year period windows of calendar time, ie, 1960-1964, 1965-1969, ..., 2010-2014. For example, in period window 2000-2004, follow-up data in the first five-year period after diagnosis are from patients diagnosed in 1995-2004 and followed up in 2000-2004. Each patient

TABLE 1 Number of patients diagnosed (N_D) in the period and the number of patients diagnosed in the preceding period, who contributed to five-year survival with a late entry (N_{LE}), posterior mean (Est), and 95% posterior interval (PI) of baseline net survival (%) at five years based on integrated nested Laplace approximation (INLA) and Markov chain Monte Carlo (MCMC) approaches, respectively, and a model with municipality specific effects by cancer site and calendar time period

Period	Ovary						Breast					
	N_D	N_{LE}	INLA		MCMC		N_D	N_{LE}	INLA		MCMC	
			Est	95% PI	Est	95% PI			Est	95% PI	Est	95% PI
1960-64	1225	346	25.7	(22.2, 29.7)	27.9	(24.0, 32.1)	3868	2198	51.4	(47.1, 55.3)	52.9	(48.9, 56.8)
1965-69	1377	535	25.3	(21.1, 29.3)	27.0	(22.6, 31.6)	4764	2704	51.0	(47.3, 54.6)	52.5	(48.8, 55.9)
1970-74	1472	584	28.9	(25.5, 32.3)	30.9	(27.1, 34.5)	6014	3383	57.9	(55.4, 60.2)	58.9	(56.4, 61.2)
1975-79	1662	673	26.8	(23.9, 29.6)	27.7	(24.6, 30.8)	7089	4498	67.5	(65.0, 69.7)	68.5	(66.0, 70.8)
1980-84	1800	668	33.6	(30.4, 36.5)	35.1	(32.2, 38.2)	8682	5618	72.5	(70.7, 74.2)	73.3	(71.6, 75.0)
1985-89	1970	874	32.7	(29.6, 35.4)	33.2	(30.3, 36.2)	11135	7079	74.3	(72.5, 75.8)	75.0	(73.4, 76.5)
1990-94	2218	970	35.4	(32.8, 37.9)	35.4	(32.6, 38.1)	12942	9248	79.9	(78.1, 81.4)	80.5	(78.9, 82.1)
1995-99	2248	1137	38.2	(35.2, 41.3)	39.2	(36.2, 42.3)	15512	11110	81.6	(80.1, 82.8)	82.0	(80.7, 83.3)
2000-04	2355	1253	45.8	(42.1, 50.0)	45.5	(41.7, 49.4)	17892	13559	86.5	(85.3, 87.4)	86.9	(85.7, 87.9)
2005-09	2266	1436	49.0	(46.4, 51.8)	49.4	(46.7, 52.3)	20096	16047	88.0	(87.1, 88.9)	88.4	(87.4, 89.2)
2010-14	2230	1435	46.2	(43.5, 49.0)	46.6	(44.1, 49.2)	22654	18202	89.9	(88.9, 90.8)	90.2	(89.3, 91.0)

contributed to one or two period windows because follow-up times were censored at five years after diagnosis. Table 1 shows the number of patients diagnosed in each period window and the number of patients diagnosed in the preceding period, who contributed to the five-year survival in the given period window with a late entry. All models considered were fitted separately for the 11 periods. Patient's age at diagnosis was categorized into five groups, ie, 0-44, 45-54, 55-64, 65-74 years, and 75 years and older. With the exception that we included children aged <15 years, these age groups are nowadays often used, for example, in the CONCORD-3⁶ (this study excluding patients 100 years or older, though) and the EURO CARE-5⁵ studies. This age grouping is also the default selection in the SEER*Stat software³⁰ provided by the Surveillance, Epidemiology, and End Results (SEER) program, and used by Corazziari et al,³¹ too, who proposed the International Cancer Survival Standard.

2.2 | Piecewise constant excess hazard model

Let $h(t)$ be the hazard of death for a patient alive at time t after diagnosis. The excess hazard of death $h_E(t) = h(t) - h_P(t)$ is the excess rate of death that the patient has compared to the rate of death $h_P(t)$ in a comparable person in the reference population. The expected hazard of death for a patient i in follow-up interval j was determined by central hospital district r_i ($r = 1, \dots, 21$), calendar year k_{ij} ($k = 1960, \dots, 2014$), and age a_{ij} in years ($a = 0, \dots, 99$), ie, $h_P(t) = \lambda_{ij} = \lambda_{r,k_{ij},a_{ij}}$.

The excess hazard $h_E(t)$ of death due to cancer was assumed to be constant within J prespecified follow-up intervals, ie, $h_E(t) = v_j$, when $t_{j-1} \leq t < t_j$, for $j = 1, 2, \dots, J$. The excess hazard v_{ij} of patient i is modeled as a multiplicative function of covariates $\mathbf{x}_{ij} = (x_{ij1}, \dots, x_{ijb})'$, such that $v_{ij} = \exp(\boldsymbol{\alpha}'\mathbf{x}_{ij})$, where $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_b)'$ is the vector of regression coefficients, in which each α_l , $l = 1, \dots, b$, is interpreted as the additive effect of the l th covariate on the logarithm of the excess hazard.

The baseline model included the age group and follow-up time (0-<4 months, 4-<12 months, and four annual intervals from one to five years) as categorical covariates. Interaction terms between the five age groups and three follow-up time intervals (0-<4 months, 4-<12 months, and 1-<5 years) were also included to allow nonproportional excess hazards by age at diagnosis. The first five years of follow up after diagnosis were considered and longer survival times were censored at five years.

The model was fitted within the framework of the generalized linear models by assuming a Poisson error for the observed number of deaths $d_{ij} \sim \text{Poisson}[(\lambda_{ij} + v_{ij})y_{ij}]$ and specifying link function $\ln(\mu_{ij} - \lambda_{ij}y_{ij})$, where y_{ij} is time at risk in interval j for patient i and μ_{ij} is the expectation of the Poisson distribution.¹⁵ The Poisson model was fitted to collapsed data $\mathbf{Y}_{mgj} = (d_{mgj}, d_{mgj}^*, y_{mgj})$, where the observed number d_{ij} and expected number $d_{ij}^* = \lambda_{ij}y_{ij}$ of deaths and time at risk y_{ij} were summed over patients in each stratum of region m (hospital district or municipality), age group g , and follow-up time interval j .

2.3 | Regional effects in excess mortality and net survival

The excess hazard of death v_{ij} may vary by hospital district ($r = 1, \dots, R$) and by municipality ($m = 1, \dots, M$) as follows:

$$v_{ij} = \exp(\alpha' \mathbf{x}_{ij} + \beta_r + u_m + v_m), \quad (1)$$

where β_r is a hospital district specific effect, u_m is structured, and v_m is an unstructured municipality-specific random effect. In our application, $R = 21$ and $M = 313$.

The parameter vectors of random effects β , \mathbf{u} , and \mathbf{v} were assumed to be mutually independent. Hospital district specific effects β_r were assumed to follow the normal distribution with mean zero and standard deviation σ_β . Unstructured heterogeneity across municipalities was modeled by multivariate normally distributed random effects v_m with mean vector of zeros and covariance as $\sigma_v^2 I$. Spatial dependencies between the municipalities were described by assuming intrinsic Gaussian conditional autoregression (CAR)³² for the multivariate distribution of random effects $\mathbf{u} = (u_1, \dots, u_M)$

$$[u_m | \mathbf{u}_{-m}, \sigma_u] \sim N\left(\frac{1}{n_m} \sum_{j \in N_m} u_j, \frac{\sigma_u^2}{n_m}\right),$$

where \mathbf{u}_{-m} denotes all components of \mathbf{u} except u_m , σ_u is the standard deviation parameter, and N_m is the set of neighbors of municipality m and n_m is the number of its neighbors. In the CAR model, if two municipalities are defined to be neighbors, their random effects are correlated, whereas random effects in nonneighboring municipalities are modeled as being conditionally independent, given the remaining random effects.^{33,34} In our application, adjacent municipalities within the same hospital district are defined as neighbors, and within each hospital district, a sum-to-zero constraint is specified on the municipality-specific random effects.

The excess mortality can be summarized in terms of the net survival index that could be interpreted, under strong assumptions, as the survival probability in a hypothetical situation where the disease would be the only possible cause of death with all other causes being eliminated.^{3,4} Although the probability interpretation may not apply, net survival is an informative and widely-used measure for cancer survival after elimination of the influence of other causes of death. The age-standardized net survival³⁵ in municipality m is the weighted average of age-specific net survival indices, ie,

$$S_E(t, r, m) = \sum_{g=1}^G w_g \exp\left[-\int_0^t v(g, u, r, m) du\right],$$

where the excess hazard is $v(g, t, r, m) = \exp[\alpha' \mathbf{x}(g, t) + \beta_r + u_m + v_m]$ and w_g is the proportion of patients in age group g ($g = 1, \dots, G$) at the beginning of follow up. The excess mortality v and net survival S_E were estimated separately in each five-year calendar period and standardized to the average distribution of patients' age at diagnosis, ie, w_g was the proportion of patients diagnosed in Finland during the whole period 1960-2014 in age group g .

2.4 | Quantifying regional variation

The amount of regional variation in each five-year calendar period was summarized by estimating (i) variation between hospital districts, (ii) variation between municipalities within hospital districts, and (iii) total variation between municipalities. The variations were quantified both in the relative excess mortality and in the five-year net survival.

Variation in the relative excess mortality was quantified on the logarithmic scale by the standard deviation s_B of the effects β_r of R hospital districts and the standard deviation s_W of the effects $u_m + v_m$ of M municipalities, respectively, ie,

$$s_B^2 = \frac{1}{R-1} \sum_{r=1}^R (\beta_r - \bar{\beta})^2 \quad \text{and} \quad s_W^2 = \frac{1}{M-1} \sum_{m=1}^M (v_m + u_m - \bar{u} - \bar{v})^2.$$

The total variation across municipalities was quantified by standard deviation s_T

$$s_T^2 = \frac{1}{M-1} \sum_{m=1}^M (\theta_m - \bar{\theta})^2,$$

where $\theta_m = \beta_{r_m} + v_m + u_m$ and $\bar{\theta}$ is the arithmetic mean of θ_m .

Variation in the age-standardized five-year net survival was quantified by standard deviations s_{SB} , s_{SW} , and s_{ST}

$$s_{SB}^2 = \frac{1}{R-1} \sum_{r=1}^R D_S(5, r, \cdot)^2, \quad s_{SW}^2 = \frac{1}{M-1} \sum_{m=1}^M D_S(5, \cdot, m)^2 \quad \text{and} \quad s_{ST}^2 = \frac{1}{M-1} \sum_{m=1}^M D_S(5, r_m, m)^2,$$

where $D_S(5, r, \cdot) = S_E(5, r, \cdot) - \frac{1}{R} \sum_r S_E(5, r, \cdot)$ is the hospital district specific deviation of the five-year net survival from the arithmetic mean over R hospital districts, $D_S(5, \cdot, m) = S_E(5, \cdot, m) - \frac{1}{M} \sum_m S_E(5, \cdot, m)$ and $D_S(5, r, m) = S_E(5, r, m) - \frac{1}{M} \sum_m S_E(5, r, m)$ are the municipality-specific deviations from the arithmetic means over M municipalities, and $S_E(5, r, \cdot)$ and $S_E(5, \cdot, m)$ are calculated by setting $u_m = v_m = 0$ and $\beta_r = 0$, respectively.

2.5 | Approximation and simulation of posterior distribution

The model was implemented in a Bayesian framework using both the INLA approach and the MCMC simulation. Vague $N(0, 1000)$ priors were assumed for the fixed effects α . For the standard deviation parameters σ_β , σ_u , and σ_v of the regional random effects, we assumed half-normal distributions centered at 0 with standard deviation 100. A half-normal and a uniform distribution were recommended by Gelman and Hill³⁶ for a diffuse but a proper prior distribution of hierarchical standard deviations and are expected to work well in general, unless the number of regions is below 5. The half-normal prior was convenient for the comparison between the two approaches by using R-INLA and OpenBUGS because it is available in both programs. For a formal discussion of weakly informative priors in this context, see articles by Simpson et al³⁷ and Riebler et al.³⁸

The joint posterior distribution is given by

$$p(\alpha, \beta, \mathbf{u}, \mathbf{v}, \sigma_\beta, \sigma_u, \sigma_v | \mathbf{Y}) \propto L(\alpha, \beta, \mathbf{u}, \mathbf{v}) p(\alpha) p(\beta | \sigma_\beta) p(\mathbf{u} | \sigma_u) p(\mathbf{v} | \sigma_v) p(\sigma_\beta) p(\sigma_u) p(\sigma_v),$$

where L is the Poisson likelihood of the entire patient population based on collapsed data $\mathbf{Y} = (\mathbf{d}, \mathbf{d}^*, \mathbf{y})$ stratified by municipality m , age group g , and follow-up time interval j

$$\ln[L(\alpha, \beta, \mathbf{u}, \mathbf{v})] = \sum_{mgj} \left\{ d_{mgj} \ln \left[d_{mgj}^* / y_{mgj} + v(\alpha, \beta, \mathbf{u}, \mathbf{v}) \right] - v(\alpha, \beta, \mathbf{u}, \mathbf{v}) y_{mgj} \right\} + \text{constant}.$$

2.5.1 | MCMC simulation

The MCMC is a simulation-based approach for computations in Bayesian inference by generating a sample of correlated values from the posterior distribution by running a Markov chain. Gibbs sampling is an MCMC algorithm that generates samples of each parameter conditional on all the other parameters. It is used, for instance, by OpenBUGS³⁹ and JAGS⁴⁰ and can be easily applied to the inference of complex models that include a large number of parameters. The well-known problem with Gibbs sampling is that subsequent values in MCMC simulation are highly correlated in hierarchical models because the random effects strongly depend on each other and also on the standard deviations of their distributions. Alternative approaches to overcome these problems include construction of a joint proposal for the full conditional distribution of random effects and updating random effect and hierarchical parameters jointly. Yet, despite these developments, MCMC sampling remains painfully slow from the end user's point of view.²⁵

In our application, the MCMC simulations were carried out by Gibbs sampling using OpenBUGS (version 3.2.3).^{39,41} Three series of 4 200 000 iterations were run. The first 200 000 iterations were discarded as burn-in in each run. Every 100th and 2000th of the remaining iterations was stored in the analyses without and with municipality-specific effects, respectively. The posterior inference was based on the pooled sample of 120 000 (analyses without municipalities) and 6000 (municipality-specific analyses) thinned values.

The coda package in R was used for the convergence diagnostic of the Markov chain and for the estimation of the Monte Carlo (MC) error. The convergence was examined by calculating the Gelman-Rubin statistic, as modified by Brooks and Gelman.⁴² The OpenBUGS program code for specifying the model in the municipality-specific analyses is included in the supplementary material.

2.5.2 | INLA approximation

As an alternative to simulation-based MCMC, INLA is a deterministic approach proposed by Rue et al²⁵ for computations in Bayesian inference on the class of latent Gaussian models, which include a wide variety of commonly applied

statistical models.²⁷ It produces accurate and fast approximations to the marginal posterior distributions based on Laplace approximations and numerical integration. The INLA approach is implemented in R-INLA package in R.²⁵

In the INLA approach, the posterior marginal distributions $p(\theta_q | \mathbf{Y})$ and $p(\psi_q | \mathbf{Y})$ of parameters $\theta = (\alpha, \beta, \mathbf{u}, \mathbf{v})$ and hyperparameters $\psi = (\sigma_\beta, \sigma_u, \sigma_v)$, respectively, are approximated by

$$\begin{aligned}\tilde{p}(\theta_q | \mathbf{Y}) &= \int \tilde{p}(\theta_q | \psi, \mathbf{Y}) \tilde{p}(\psi | \mathbf{Y}) d\psi \quad \text{and} \\ \tilde{p}(\psi_q | \mathbf{Y}) &= \int \tilde{p}(\psi | \mathbf{Y}) d\psi_{-q},\end{aligned}\tag{2}$$

where subscript q refers to the q th component of the corresponding vector (θ or ψ) and $-q$ to the vector without the q th component. The Laplace approximation of the joint posterior of the hyperparameters is denoted by $\tilde{p}(\psi | \mathbf{Y})$ and the simplified Laplace approximation was used for $\tilde{p}(\theta_q | \psi, \mathbf{Y})$. The first integral (2) can be solved numerically through a finite weighted sum

$$\tilde{p}(\theta_q | \mathbf{Y}) \approx \sum_k \tilde{p}(\theta_q | \psi^{(k)}, \mathbf{Y}) \tilde{p}(\psi^{(k)} | \mathbf{Y}) \Delta_k\tag{3}$$

over some relevant integration points $\{\psi^{(k)}\}$ with a corresponding set of weights $\{\Delta_k\}$.^{25,43} Rue et al²⁵ proposed two different strategies to identify the integration points for exploring the joint posterior of the hyperparameters $\tilde{p}(\psi | \mathbf{Y})$. In the grid integration strategy, the joint posterior is evaluated in a regular grid of points. The other one is called central composite design (CCD) strategy and reduces the computational costs by using much fewer integration points, these being located on a sphere around the mode.²⁷

In addition to providing approximations to posterior marginals of model parameters θ_q and ψ_q , R-INLA includes tools to draw samples independently from an approximated full posterior distribution that can be used to estimating the functionals of model parameters θ . The sampling makes use of the values $\tilde{p}(\psi^{(k)} | \mathbf{Y})$ of the joint posterior of hyperparameters and the joint Gaussian approximation of $\tilde{p}(\theta | \psi^{(k)}, \mathbf{Y})$ that were already computed for the grid points $\{\psi^{(k)}\}$ in the numerical integration (3). The sampling algorithm has the following two steps.

1. Sample hyperparameters ψ^* from the set of $\{\psi^{(k)}\}$ with probabilities $\tilde{p}(\psi^{(k)} | \mathbf{Y}) \Delta_k$ computed in the numerical integration (3).
2. Conditional on the sampled ψ^* , sample θ^* jointly from the corresponding joint Gaussian approximation of $p(\theta | \psi^*, \mathbf{Y})$, which was already calculated in the numerical integration (3) to obtain the approximation $\tilde{p}(\psi^* | \mathbf{Y})$ to the joint posterior of the hyperparameters. Here, however, an improved approximation using a Gaussian copula⁴⁴ that retains the dependence structure of the Gaussian approximation of $p(\theta | \psi^*, \mathbf{Y})$ while having the improved approximations of the marginals $p(\theta_q | \psi^*, \mathbf{Y})$ is used.

In our application, the model was fitted by using `inla` function in R-INLA package²⁵ with the default CCD integration strategy. Then, the grid integration strategy was utilized to improve the estimates of the posterior marginals of the hyperparameters by using `inla.hyperpar` function. The posterior estimates were based on a sample of 3000 values drawn independently from the approximated posterior distribution by using `inla.posterior.sample` function. The program code for fitting the model in the municipality-specific analyses is included in the supplementary material.

3 | RESULTS

3.1 | Computation time

In the MCMC approach, computation time was based on the number of iterations required to obtain the MC errors of 5% or less out of the standard deviations of target parameters s_B , s_W , and s_T ; 260 thousands and 1.1 million iterations in the analyses without and with municipality-specific effects, respectively. In R-INLA, parallel computing with four threads was utilized.

In the model without municipality-specific effects, the analyses of ovary and breast cancer took altogether 2.1 minutes with the INLA and 100 minutes with the MCMC approach (based on the 5% level of MC error). When the effects of municipalities were included in the model, computation time increased to 1.6 hours and 400 hours in the INLA and the MCMC approach, respectively. If the number of threads was limited to one in R-INLA, the analyses took 3.25 hours. In the INLA approach, the posterior sampling part took 61% and 29% out of the total computation time in the models without and with municipality-specific effects, respectively.

In the following, results are based on the total number of stored iterations with MC errors of 1.4% or less out of the standard deviations of the parameters.

3.2 | Regional variation

Figure 1 compares the estimates of the standard deviations s_B and s_{SB} between the INLA and the MCMC approach in the model without municipality-specific effects. The posterior means and 95% posterior intervals were very similar between the two approaches. In ovarian cancer, the standard deviations were relatively large in 1965-1969 and in 2000-2004. In breast cancer, the standard deviations decreased from the 1960s to the 1980s. From 1990s, the variation in the relative excess mortality has not decreased even though it has decreased on the scale of five-year net survival.

Figure 2 compares the estimates of the standard deviations s_B , s_W , and s_T between the INLA and the MCMC approach in the model in which the effects of municipalities are also included. The estimates of INLA are close to those of MCMC simulation. The standard deviation s_B is smaller than that based on model without municipality. Variation within hospital districts dominated in the total variation. We estimated the average of variation over the last three five-year periods for obtaining a more precise estimate. In 2000-2014, the average of variation s_W^2 within hospital districts was 68% (95% posterior interval: 35-93%) and 82% (60-98%) out of the total variation s_T^2 in ovarian and breast cancer, respectively. Supplementary Figure S2 shows the standard deviations in the five-year net survival.

The close similarity in the estimates of standard deviations between INLA and MCMC (Figures 1 and 2) was based on the improved estimates obtained by using the grid integration strategy in INLA. By using the CCD integration in INLA, the posterior means were overestimated on average by 15% and the posterior intervals were up to 29% shorter because the lower limits of the intervals were clearly overestimated.

Although the estimates of the standard deviations were similar, the posterior means of the baseline of five-year net survival based on INLA was most often smaller than that based on MCMC. The largest difference was 2.2 percentage points (pp) in the municipality-specific analysis of ovarian cancer in 1960-1964 (Table 1). In the analysis without municipality (Supplementary Table S1), the differences between INLA and MCMC were on average 33% smaller than those in municipality-specific analysis. The regional estimates of five-year net survival based on the INLA approach are shown in Figure 3. In ovarian cancer, there was more variation between hospital districts in the end of 1960s and in the beginning of 2000s. However, the capital of Finland was divergent in 2000s but not in 1960s. Figure 4 shows the regional estimates of five-year net survival in 1960-1964 and in 2010-2014 divided by hospital districts to assess variation within each hospital district.

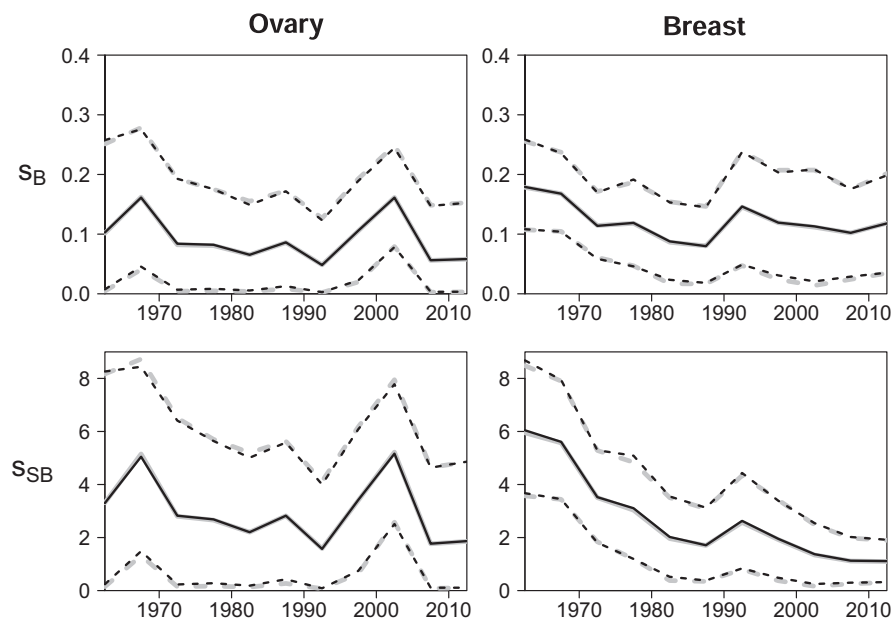


FIGURE 1 Estimates of INLA (black) and MCMC (gray) based on model (1) without municipality-specific effects: posterior means (solid lines) and 95% posterior intervals (dashed lines) of the standard deviations s_B and s_{SB} (in percentage points) in female patients diagnosed with cancers of ovary and breast in Finland and followed in five-year periods from 1960-1964 to 2010-2014. INLA, integrated nested Laplace approximation; MCMC, Markov chain Monte Carlo

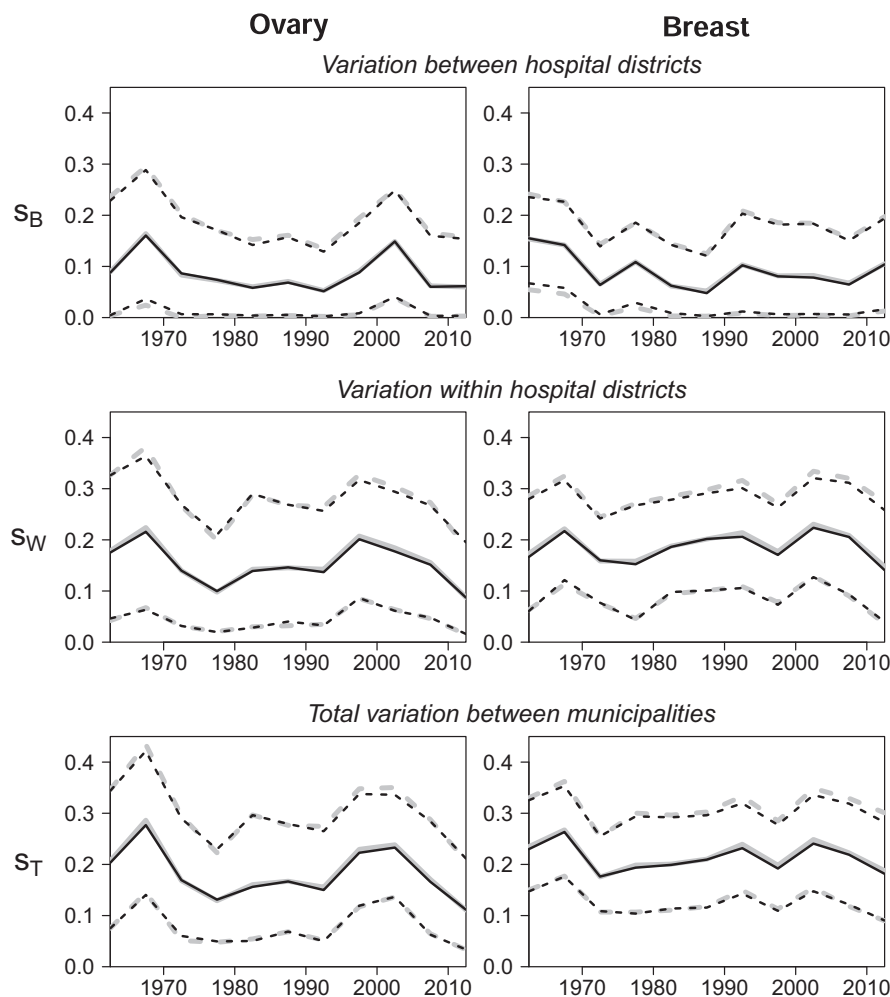


FIGURE 2 Estimates of INLA (black) and MCMC (gray) based on model (1) that includes both hospital district and municipality specific effects: posterior means (solid lines) and 95% posterior intervals (dashed lines) of the standard deviations s_B , s_W , and s_T in female patients diagnosed with cancers of ovary and breast in Finland and followed in five-year periods from 1960-1964 to 2010-2014. INLA, integrated nested Laplace approximation; MCMC, Markov chain Monte Carlo

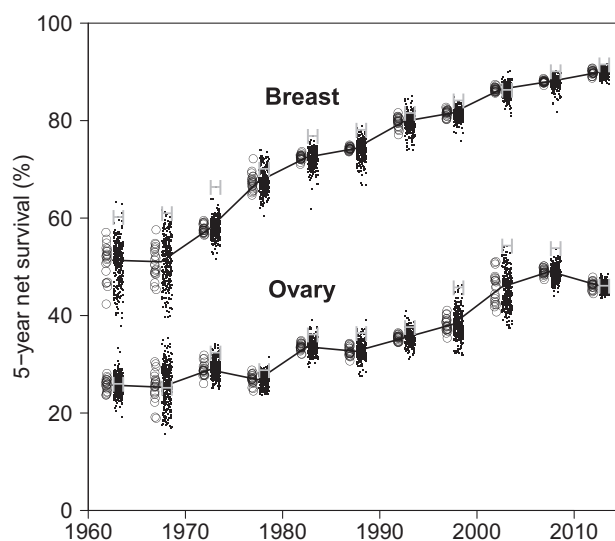


FIGURE 3 Posterior means of five-year net survival by hospital districts (open circles) and municipalities (black dots) of patients diagnosed with cancers of ovary and breast in Finland and followed in five-year periods from 1960-1964 to 2010-2014 based on INLA. Capital letter H shows the estimate of patients diagnosed in the capital of Finland, Helsinki

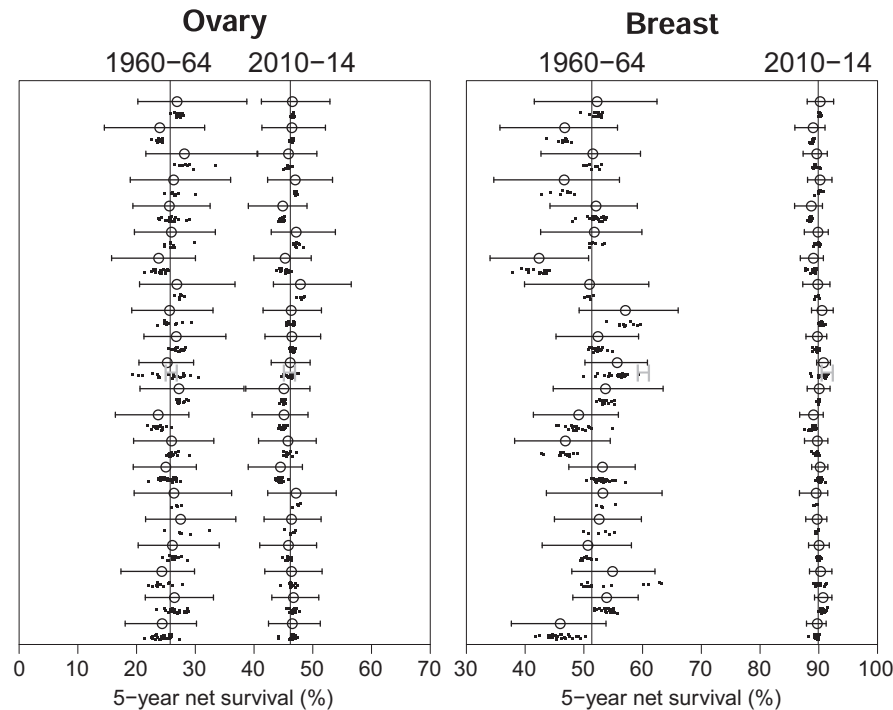


FIGURE 4 Posterior means of five-year net survival by hospital districts (open circles) and municipalities (black dots) of patients diagnosed with cancers of ovary and breast in Finland and followed in 1960-1964 and in 2010-2014 based on INLA. Horizontal lines show 95% posterior intervals of five-year net survival in hospital districts, and capital letter H shows the estimate of patients diagnosed in the capital of Finland, Helsinki

3.3 | Simulation study on bias in estimators of baseline excess mortality

A simulation study was performed to compare the INLA and the MCMC approach in the estimation of baseline excess mortality $v_{ij} = \exp(\alpha'x_{ij})$ because the baseline estimates differed between the approaches. Altogether, 1000 datasets were generated from the Poisson distribution by using the observed numbers of deaths in ovarian and breast cancer patients as the expected values in each stratum of age group, follow-up time interval, and calendar time period (categorized similarly as earlier in Sections 2.1 and 2.2).

Excess mortality was summarized in the terms of the net survival index. The MCMC and the INLA estimators of five-year net survival were compared with the maximum likelihood estimator (MLE) in two different baseline models.

- M1. A full model that included a parameter for each stratum of age group and follow-up time.
- M2. A simplified model in Section 2.2, which assumed the same interaction effect of age and follow-up time in the intervals of follow-up time from 1 to 5 years.

The bias, variance, and mean squared error were calculated and, in the INLA and the MCMC approach, were based on the posterior means. The MCMC approach was carried out using JAGS program (version 4.1.0)⁴⁰ and was based on 110 000 iterations of which the first 10 000 samples were discarded as burn-in.

The expectation of MLE was between the expectations of INLA and MCMC in the simulation setting of ovarian and breast cancer (Supplementary Figures S3-S6). In the age-standardized five-year net survival, the absolute differences between INLA and MLE were about the same as those between MCMC and MLE.

In the full baseline model (M1), from which the datasets were generated, the MLE was practically unbiased (Supplementary Figures S3 and S5). In ovarian cancer, the MCMC approach overestimated the age-standardized net survival on average by 0.8 pp, whereas the INLA approach underestimated the survival on average by 1.6 pp. In breast cancer, MCMC overestimated and INLA underestimated the survival on average by 0.4 pp and 0.6 pp, respectively.

In the simplified baseline model (M2), also the MLE was slightly biased (Supplementary Figures S4 and S6) because the datasets were generated on the basis of observed mortality rates. The magnitudes of bias related to the MCMC and the INLA approach were clearly smaller than those in the full baseline model, especially in ovarian cancer. The MCMC

overestimated the net survival on average by 0.2 pp in ovarian and 0.1 pp in breast cancer. The INLA underestimated the corresponding quantities on average by 0.3 pp and 0.2 pp.

In the age group specific estimators of the five-year net survival, the INLA approach introduced some bias in every age group, whereas the MCMC approach was biased mainly in the two oldest age groups. The largest values of bias were related to small number of deaths (d_{mgj}) or excess deaths ($d_{mgj} - d_{mgj}^*$) in an interval of follow-up time. The posterior distribution of the logarithm of excess mortality based on the MCMC simulations had a heavy lower tail if the number of excess deaths was small. This resulted in the overestimation of net survival. On the other hand, the posterior approximation based on the INLA was symmetric and poor (supporting large values of excess mortality), if the number of deaths was small, and especially, if it was smaller than the expected number d_{mgj}^* . This resulted in the underestimation of net survival.

4 | DISCUSSION

In this study, we demonstrated and validated the use of the INLA approach for the estimation of regional variation in excess mortality and relative or net survival. The study showed that the estimates of regional variation were similar based on the INLA and the MCMC simulations, and the results were obtained much faster by using the INLA than the MCMC approach. The simulation study based on the model without random effects showed that both approaches introduced some bias in the estimation of baseline excess mortality, but the magnitude of bias was most often modest.

Small variation in survival between hospital districts does not imply regional equity because there may be substantial variation within hospital districts. The variation within hospital districts is influenced by differences in personal health behavior and in primary health care. The former one includes person's ability to seek medical care and person's health status, which affects the available treatment options. The latter one includes the availability of health care services and delays in the patient path from primary care to the central hospital.

The same determinants that cause variation in survival within hospital districts cause variation between hospital districts if the distributions of the determinants differ between hospital districts. In addition to these determinants, variation between hospital districts is affected by differences in cancer care provided by the central hospitals and university hospitals.

Spatial correlation in survival across municipalities was considered important, as it is likely that many determinants of survival exist that correlate between neighboring municipalities. Information on geographical proximity between hospital districts was not incorporated in the models because patients in a given municipality are treated in a designated central hospital and further referred to the pertinent university hospital, if more advanced care is needed.

Patients' mortality was compared to the population mortality in the corresponding hospital district. Although the reference population also includes cancer patients under study, this can usually be considered to have a negligible effect on the estimated net survival.⁴⁵ In prostate cancer and especially in all cancer sites combined, an adjustment for the reference population mortality has been recommended.^{46,47} This adjustment was not done, for example, in the EURO-CARE-5 and the CONCORD-3 study,^{5,6} either. In our application, the five-year net survival is likely to be overestimated approximately by 0.7 pp in breast cancer and less than that in ovarian cancer according to the results of Talbäck and Dickman.⁴⁶

Considering hospital district-specific population mortality rates to be fixed without random variation was shown to be a reasonable assumption for the estimation of excess mortality.⁷ However, variation in excess mortality within hospital districts includes variation due to potential differences in population mortality between municipalities within each hospital district. In municipality-specific population mortality rates, random variation should be taken into account by using an extended model that includes the likelihood for population mortality.⁷

Standard deviations s_B , s_W , and s_T quantify how much there is variability in the logarithm of relative excess mortality across regions. This variation can remain at the same level, even though regional variation in net survival decreases, as it happened in breast cancer in Finland. Interpretation of both measures depends on the average level of excess mortality and net survival. The choice of the measure is ultimately based on the decision on whether we shall count the failures or the successes and whether we shall make relative or absolute comparisons.⁴⁸ The standard deviations s_{SB} , s_{SW} , and s_{ST} of net survival may have more attractive interpretation because net survival is commonly used for summarizing excess mortality among cancer patients.^{5,6}

An increased regional variation in the survival of ovarian cancer around year 2000 was shown by Pohar Perme et al⁴⁹ in the study that assessed variation between the five cancer control regions in Finland in 10-year periods of diagnosis from 1953-1962 to 1993-2002. Our study showed that the increased difference was more related to the variation between the hospital districts than to the variation within them and that the regional variation decreased thereafter.

The decrease in the standard deviation of the net survival in breast cancer does not indicate that the public health importance of regional variation has decreased because breast cancer incidence increased simultaneously. When assessing the public health importance, the changes in incidence can be taken into account, for example, by estimating potential numbers of person years or deaths that would be saved, if regional variation were eliminated.⁷

We estimated the finite population variances because the data were collected from all the 21 hospital districts and 313 municipalities in Finland and we wish to describe the variation across these very districts. Alternatively, variation may be measured by estimating the so-called superpopulation variance, ie, the theoretical variance of the distribution of the random effects would be appropriate for assessing the uncertainty about the value of a potential new district not in the original set.³⁶ The posterior mean of the superpopulation standard deviation σ_β was on average 7% larger than that of the finite population s_B . The 95% posterior intervals for σ_β were from 14% to 27% wider than those of s_B . The superpopulation variance of municipalities is not directly obtained because the standard deviation σ_u of the CAR model is not comparable with that σ_v of the unstructured effect. However, the intrinsic CAR model can be scaled, such that the conditional variance will be equal to the marginal one.⁵⁰

Censoring all follow-up times at five years may affect the results of regional variation if notable excess mortality exists and varies across regions after the first five years since diagnosis. Quite often, follow up is considered only up to the first five years because, thereafter, excess mortality typically becomes small. Among breast cancer patients, however, the mortality remains elevated even beyond five years compared with the reference population,⁵¹ and therefore, including a longer-term follow-up could have an effect on regional variation.

Excess hazard was assumed to be constant in each follow-up time interval according to model (1). We divided the first year of follow-up into four- and eight-month intervals because excess mortality changed most rapidly in the beginning of the follow up especially among ovarian cancer patients. In addition to incorrectly specified functional form, the model may suffer from lack-of-fit due to omission of important unmeasured covariates (ie, overdispersion) or absence of important interaction terms.¹⁵ Overdispersion may occur if important determinants of cancer survival are omitted in the model. For example, tumor stage and patient's health status at the time of diagnosis and information on whether a patient participated in mammography screening are such covariates that may cause overdispersion. According to a score test for overdispersion proposed by Luque-Fernandez et al,⁵² no statistically discernible overdispersion could be observed for all periods combined. However, some evidence for overdispersion was found in some periods, ie, 1990-1994 in breast and ovarian cancer and in 2005-2009 in ovarian cancer (analyses without municipality); and 1990-1994 and 2000-2004 in breast cancer (municipality-specific analyses). In addition, we did a sensitivity check by including an additional stratum-specific random effect in the model to adjust for potential overdispersion. The effect of adjusting for overdispersion was small. By including the overdispersion effect in the model without municipalities, posterior mean of s_B decreased on average by 3% in ovarian cancer and by 5% in breast cancer and the length of the posterior interval increased by 3% and by 5%, respectively. In the municipality-specific model, the overdispersion-adjusted estimates differed from the nonadjusted ones less than 3%.

Stratifying the calendar periods into five-year periods and modeling them separately were a convenient choice because the intrinsic CAR model was available in R-INLA and OpenBUGS. It would be difficult to select particular break points at which some actions related to cancer survival occurred. In addition, a temporal structure that would remain valid over the long 55 years calendar period was not plausible. Spatio-temporal models become easily complex, and the challenge is to find a sufficiently realistic yet manageable model that includes necessary interactions. R-INLA includes spatio-temporal models with a first- or second-order random walk structure for the temporal effect and several options for space-time interactions.^{43,53} We also tried to fit a spatio-temporal model where we assumed a second-order random walk across the 11 calendar periods for each hospital district independently. In addition, we tried to fit another spatio-temporal model where the temporal dependence structure of each municipality depends on the temporal patterns of the neighboring municipalities. However, we did not succeed to fit the models with municipality-specific effects due to memory limitations in our computation environment. The only model that converged (without the grid integration strategy in INLA) was a model without municipality-specific effects in breast cancer. There is an ongoing work within the R-INLA project to improve this limitation.

INLA has shown to give very accurate approximations to the posterior marginals of the model parameters over a wide range of commonly used latent Gaussian models including generalized linear mixed models.^{25,54} In this study, we were interested in the posterior estimates of functionals of model parameters rather than the posterior marginal distributions of the parameters. For example, presenting variation on the scale of net survival requires the joint posterior of the all model parameters except the variance parameters. In our application, the sampling algorithm implemented in R-INLA package for generating samples from an approximated posterior proved to be very accurate to estimating these functionals.

INLA and MCMC approaches introduced some bias in the estimation of the baseline excess mortality. The model itself may introduce bias because it does not allow negative excess mortality. However, because the MLE was practically unbiased, the bias in the MCMC approach relates to the prior assumption that becomes informative because of the model and its likelihood, which is greater than 0 for excess mortality $\nu = 0$. Therefore, a flat normal prior for the logarithm of excess mortality may result in posterior $p[\ln(\nu) | \mathbf{Y}]$ with a heavy negative skew, if the number of deaths is small, because small values of excess mortality are supported by the prior. The INLA approximation, on the other hand, may not catch the shape and the spread of the negatively skewed posterior and may therefore support too large values of excess mortality. Results based on the simplified baseline model (M2) show that the bias may be reduced by excluding some interaction terms between follow-up time and age if the simplified model still fits the data well. The previous study of Saez et al²² that used a similar model and MCMC simulation did not explore the potential bias. The model included the main effects of follow-up time and age only. This is, however, often invalid assumption in cancer survival, and therefore, may not reduce bias.

In the MCMC estimation, the convergence has to be explored carefully. In our application, the mixing of the Markov chain was very slow especially in the municipality-specific effects and their standard deviations. A large number of iterations were run to achieve negligible Monte Carlo errors. A clearly smaller number of iterations satisfied the 5% level of MC error suggested in the OpenBUGS manual,³⁹ but the computation time was still from 48-fold to 250-fold in the MCMC approach compared to the INLA approach. This is in line with other applications of hierarchical Poisson model implemented in R-INLA and OpenBUGS⁵⁵ or WinBUGS,⁵³ as these other implementations did not utilize the grid integration and the posterior sampling of INLA that were necessary in our application.

In the estimation of regional variation in excess mortality of ovarian and breast cancer patients in Finland, the INLA approach was accurate, fast, and easy to implement by using the R-INLA package. It can be recommended for routine use in monitoring regional variation in excess mortality and net survival.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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