Spatial analysis of breast and cervical cancer incidence in small geographical areas in Cuba, 1999-2003

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Title: Spatial analysis of breast and cervical cancer incidence in small geographical areas in Cuba, 1999-2003.

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Abstract.

Background: According data from the National Cancer Registry (NCR), breast and cervix cancer are the two most common non-skin cancers in Cuban woman. This study was addressed to describe the geographical variation of their incidence at small area level over the period 1999-2003. **Methods:** For each municipality, standardised incidence ratios (SIR) were calculated and smoothed using a Poisson-Gamma, Poisson-Lognormal (PL) and a Conditional Autoregressive (CAR) model. The covariate 'urbanisation level' was included in the PL and CAR models. The posterior probability of each municipality's relative risk (RR) exceeding unity was computed. Clusters were confirmed using the Spatial Scan statistic of Kulldorff. **Results:** The CAR model provided the best fit for the geographical distribution of breast and cervix cancer in Cuba. For breast cancer a high risk region was identified in municipalities of Ciudad de La Habana province (CAR-smoothed RR between 1.21 and 1.26). Cervical cancer exhibited two areas with excess risk on the eastern and extreme-west of the island (CAR-smoothed RR range 1.2 to 2.01 both areas together). Clusters were confirmed only for cervical cancer (p=0.001 for the most likely cluster and p=0.003 for a secondary cluster). **Conclusions:** The study supports the hypothesis of a spatial variation in risk at small-area essentially for cervical cancer and also for breast cancer that probably reflects the territorial distribution of life style and socioeconomic factors. This is the first attempt to introduce this methodology in the framework of the NCR of Cuba and we expect to extend their use to forthcoming analyses.

Key Words: spatial analysis; breast cancer, cervical cancer; cancer incidence; small area studies; Bayesian models; geographical distribution.

Introduction.

Breast and cervix cancers are the two most common non-skin cancers in Cuban women and represent around the 18% and 10% respectively of the total diagnosed cancers in females in the country (MINSAP / DNE, 2006; Torres et al., 2007). According to data of Globocan 2002 (Ferlay et al., 2004), the age-standardized incidence and mortality rates of both breast and cervix cancer in Cuba ranked among the lowest in the Caribbean. Breast cancer incidence is higher than in Central America and intermediate-lower compared with South America countries. Cervix cancer incidence is lower than in Central and South America (excepting Uruguay).

In Cuba, around 28,000 new cancer cases are diagnosed each year and more than 18,000 people died as a result of cancer, representing 23% of all deaths. In terms of incidence, cancer in women accounts for 48% of the total cancer cases yearly diagnosed.

~~As a part of the National Program for Cancer Control, the National Programs for Early Detection of Breast and Cervix Cancers have been implemented, since 1989 and 1967, respectively (Camacho et al., 1994).~~ As a part of the National Program for Cancer Control, the National Program for Early Detection of Breast Cancer started in 1987**.** At the beginning the program's policy was to promote breast self-examination in women over 30 years-old, and an annual examination by family doctors. Mammography screening was introduced in 1989-90, in addition to the two physical examinations, but stopped later in 1995 due to lack of mammography and other related equipments (Fernandez et al., 1994; Camacho, 2003). A Cervical cytology Screening Program, offering pap smears every two years to women aged >=20 years, was implemented through the primary health care services in 1968. It has been suggested that more than 80% of Cuban women aged 20–60 years have been screened at least once (Camacho et al., 1994; Fernandez et al., 1996). Both programs, as organized through the primary health care system were evenly distributed across the country;

Neverthelessnonetheless, these are still being two important public health problems in the country.

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Previous descriptive analysis based on the National Cancer Registry (NCR) of Cuba at a provincial level suggested the hypothesis that breast and cervix cancer risks show important geographical differences between the western and eastern part of the island (Galan et al., 2003; Torres et al., 2007). However, these comparisons are insufficient to provide realistic and useful criteria for a rational determination of priorities in terms of resource allocation and identification of areas of unusually high risk. The introduction of studies addressed to investigate health inequalities of smaller geographic units constitute at present a genuine challenge for the Cuban Cancer Registry.

The main goal of this paper is to describe the geographic distribution of breast and cervix cancer incidence over the period 1999-2003 in Cuba.

Methods.

Data from NCR included on average 2,438 and 1,451 new cases of breast and cervix cancer observed annually among female population over the period 1999-2003, which have been histologically or cytologically confirmed. Details on the structure and procedures of the NCR have been published before (Martin et al., 1998). A pool of the last 5 years available data at NCR was done in order to minimize the effect of the random fluctuations observed in the number of cases reported from one year to another.

The country is divided into 169 municipalities, with a female population of 33,200 on average per municipality in 2001, ranging between 4,278 and 245,484 people. For each municipality the annual numbers of new breast and cervix cancer cases were recorded, as well as the population counts in 5-years age groups. Data on the population sizes were provided by the

National Office of Statistics. The latitude and longitude from the centroid of each municipality was supplied by the Institute of Geography.

Statistical Methods

The standardized incidence ratio (SIR) for each municipality (i = 1,...,169) was calculated as (Jensen et al., 1995):

$$SIR_i = \frac{O_i}{E_i} = \frac{\sum_a O_{ia}}{\sum_a \left(\frac{O_{ia}}{n_{ia}}\right) n_{ia}}$$

where O_{ia} denotes the number of cases in municipality i and age group a, and n_{ia} is the corresponding number of individuals at risk. The expected value E_i is calculated by applying the overall age-specific rates of Cuba over the five year period to each study region. Confidence intervals (CIs) for the SIRs were calculated using the method of Ury and Wiggins (1985).

To overcome the main drawbacks in the use of SIRs for map presentation, stemming from instability resulting from varying population size, a full Bayes approach was used to provide smoothed estimates of relative risk (RR) for each of the 169 municipalities. A summary on Bayesian inference for RRs is given in e.g. Maiti (2005). An application and short summary is given in Buntinx et al. (2003).

We consider here three models: Poisson-Gamma, Poisson-Lognormal and Conditional Autoregressive (CAR).

In these models the initial assumption is the Poisson distribution of the observed counts

$$O_i \sim Poisson\ (E_i r_i)$$

where E_i the expected counts and r_i the true (underlying) RRs; the extra-Poisson variation is incorporated by assuming that the true relative risks follow an a priori common statistical distribution on positive values. Two types of priors on r_i are assumed: a spatially independent prior and a spatially structured prior.

Among the existing candidates, we first used the gamma and lognormal priors, both being spatially independent. While the gamma prior is numerically advantageous, the lognormal prior is less restrictive due to the option of covariate adjustment. An important drawback of Poisson-gamma and Poisson-lognormal models is the fact that they do not allow for spatial dependence; actually prior knowledge may indicate that geographically close areas tend to have similar RRs. As an alternative we made use of the model developed by Besag et al. (1991); being a random effects Poisson model allowing for overdispersion and spatial correlation, using a conditional autoregressive (CAR) prior (Buntinx et al., 2003). This CAR prior is spatially structured. With this model, SIRs are smoothed locally towards the mean risk in the set of neighbouring areas.

Conditional autoregressive priors for r_i are given by:

$$r_i|r_j\ (j \neq i) \sim N(m_i,\ v_i)$$

where $m_i = 1/n_i \sum r_j$, *with* $j \in \delta_i$. In this definition, δ_i is the set of adjacent areas of i, n_i is the number of neighbours of area i, and $v_i = v_v / n_i$ is the variance.

That is, in each municipality, the resulting estimated risk is a combination of the specific municipality rate and the rates in neighbouring wards. In other words: r_i is smoothed towards the local average risk in a set of neighbouring areas, with variance inversely proportional to the number of neighbours.

Additionally, the level of urbanization for each municipality was included as a covariate in the CAR model and the log-normal model as well. This variable is calculated as the percentage of the population living in the urban sector of the municipality and was supplied by the National Office of Statistics.

All models were implemented using WinBUGS 1.4 (Spiegelhalter et al., 2003). The adjacency matrix required for the CAR model was constructed using a detailed cartographic representation of the municipalities in the country and its neighbourhoods.

The posterior distributions for all parameters in the models were estimated via Gibbs sampling. Each Markov chain consisted of 15,000 iterations, following a burn-in period of 1,000 iterations. The convergence was checked by trace plots and autocorrelation plots.

To compare models, the Deviance Information Criterion (DIC) was used, which enables simultaneous assessment of goodness-of-fit and model complexity (Spiegelhalter et al., 2002). The raw SIRs and the estimated (or smoothed) RRs obtained with the best Bayesian fit were mapped using a grey scale, based on a uniform log-scale division similar to the suggestion of Knorr-Held and Rasser (2000) and subdivided in 7 categories. Dark regions indicate a high risk of disease whereas light regions indicate a small risk.

Moreover, the posterior probability of each municipality's RR exceeding unity was calculated and mapped providing a measure of the strength of (statistical) evidence of excess risk in each ward. High probabilities can be interpreted as providing clear evidence of an excess risk, while low probabilities are related to regions with no excess risk (Jarup and Best, 2003; Jarup et al. 2002; Richardson et al. 2004).

All maps were created using a Geographic Information System MapInfo Professional, version 8.5. For a better representation of the province Ciudad de La Habana, the capital of Cuba with more than 2 millions of inhabitants and including 15 municipalities, a zoom was made.

Finally, the standard purely spatial scan statistic of Kulldorff (Kulldorff M, 1997), implemented in the SaTScan software (Kulldorff M and Information Management Services, Inc; 2008) was used for the confirmation of suspected clusters with increased risk identified in the analysis of the smoothed RR obtained with the best Bayesian fit (Buntinx et al., 2003). The Scan statistic is based on the imposition of circular or elliptical windows on the map which are in turn centred on each of several possible grid points positioned throughout the study region. For each grid point, the radius of the window varies continuously in size from zero to some upper limit typically set at 50% of the geographical study region. For each location and size of the scanning window, the alternative hypothesis is that there is an elevated risk within the window as compared to outside. The likelihood function is maximized over all window locations and sizes, and the one with the maximum likelihood constitutes the most likely cluster. In addition SaTScan identifies secondary clusters that could be of interest mostly in case of not overlapping with the most likely cluster (Kulldorff M, 2006). In our analysis, an elliptic window shape was selected and for breast cancer data, the covariate urbanization level was also included in this analysis.

Results.

Table 1 summarizes the model diagnostics for breast and cervix cancer in Cuba. For both localisations the best fit was obtained with the CAR model, having the lowest DIC. The inclusion of the covariate urbanization level improves this result for breast cancer.

The posterior CAR-relative risk estimates for breast cancer in the 169 municipalities of Cuba range from 0.46 to 1.26, whereas for cervix cancer it varies from 0.68 to 2.02. Unsmoothed and CAR-smoothed relative risks for localities having risk estimations of above 1.2 or, a posterior probability (based on the smoothed model) of at least 0.90 that their estimated RR would be higher than 1, are summarized in Tables 2 and 3. These criteria were used to select a reasonable number of municipalities (from a total of 169) with some evidence of an excess risk.

Maps of crude and smoothed SIRs and maps of the posterior probabilities of relative risks exceeding unity are showed in Figures 1 and 2.

Estimates of the relative risk show less variation than the observed SIR as can be expected after Bayesian smoothing. Whereas in maps of crude SIRs no clear patterns are elucidated in the distribution of risk (Figures 1a & 2a), the smoothed maps provide well delimited homogeneous areas in which different geographic risk configurations could be distinguished.

For breast cancer a region with a moderated higher risk (CAR smoothed RR varying from 1.21 to 1.26) is observed in municipalities of Ciudad de La Habana province and in two adjacent districts located in the neighbouring province of Matanzas (Table 2, Figure 1b). The RR estimated had in these cases a probability of above 0.99 to be greater than unity (Figure 1c). Additionally, nine non-adjacent municipalities dotted around the country, mainly corresponding to provincial towns, had also estimated RR greater than unity with at least 90% probability (smoothed RR between 1.09 and 1.17). Otherwise, Figure 1c provides evidence of a slightly reduced risk of breast cancer and no statistically significant cluster was identified by the spatial scan statistic of Kulldorff.

Cervix cancer incidence exhibits two regions with excess risk. A major area in the east with RR estimates varying from 1.2 to 1.58 that covers the 59% of the 54 wards comprised in the five oriental provinces as well as two neighbouring municipalities of Camaguey province. And, an excess risk area of a minor size confined to the most extreme western side in the province of Pinar del Rio, which encompasses seven municipalities (RR estimates between 1.21 and 2.01) (Table 3, Figure 2b). In contrast, lowest risks (between 0.6 – 0.8) are observed in the central - western part of the country (Figure 2b).

The posterior probability of the estimated RR being superior to 1 is of 0.90 or more in 37 of the total of 41 municipalities with smoothed RR of at least 1.20 as well as in the municipality of Santiago de Cuba city (estimated RR of 1.14) (Figure 2c). For the remainder of the municipalities included in these high risk regions this probability was estimated on 0.83.

The spatial scan statistic of Kulldorf confirms findings described with the CAR model and identified a subset of 20 municipalities from the east side high risk region as the most likely cluster (p=0.001, Table 3). In a secondary statistically significant cluster (p=0.003) the municipality of Sandino was included (highest CAR smoothed RR overall).

Discussion.

This study supports the hypothesis of a spatial variation in risk for breast and cervical cancer in small areas in Cuba during the 5-year period 1999-2003. However, geographical differences in risks were more marked for cervical cancer and statistically significant clusters were detected in this case. Furthermore, patterns of excess-risk areas were somewhat complementary between these two diseases.

Awareness about the interpretation of geographical variations has been highlighted in previous publications (Jarup et al., 2002). A tentative partial explanation for the differences observed in the present study could be the disparities in local implementation of Programs for Early Detection of Breast and Cervix Cancers. However, this hypothesis seems to be not plausible (… seems to be slightly plausible and could be practically discarded). In fact, the needs in terms of financial and technological resources in mid-90's imposed serious limitations in the mammography use just some few years once their recommendation as a part of the national screening policy (Camacho et at., 2003). On the other hand, as it has been expressed in a previous publication, the cervical cytological screening program in Cuba has showed a very limited impact on the incidence of cervical cancer despite the large numbers of cytological smears taken in the country (Sankaranarayanan et al., 2001).

Therefore, the existing information on geographical distribution of risk factors even if limited to provincial level, permits us to consider more plausible the possibility that the raised-risk areas observed in the present study could reflect the territorial distribution of life style and socioeconomic factors.

~~In the context of this study, differences observed could be partially explained by disparities in local implementation of Programs for Early Detection of Breast and Cervix Cancers, also there is probably some variation due to differences in data collection and timeliness in provincial registries.~~

~~Nonetheless, the existing information on geographical distribution of risk factors even if limited to provincial level, permits us to consider the possibility that some of the raised risk areas could also probably reflect the territorial distribution of life style and socioeconomic factors.~~

A survey conducted in 1994 described a number of demographic, life style (sexual and reproductive behaviours, alcohol and tobacco consumption) and socioeconomic factors among provinces of Cuba. The study determined, via a multivariate analysis, that the female population in the oriental region of the country was characterized by an earlier age of initiation of sexual activity and a broader history of gynaecological pathologies compared with those of the centro-occidental region (Lorenzo-Luaces et al., 1995). Since it has become established that certain sexually transmitted types of human papillomavirus (HPV) are a necessary cause for cervical cancer, it seems that most of these factors are surrogates for HPV infection (Bosch et al., 2002; Arrossi et al., 2003). However, it is very difficult to establish whether the observed variations are due to differences in prevalence of HPV infection. In recent work of the IARC HPV Prevalence Surveys Study Group, data from population-based HPV surveys in world-regions of low, intermediate, and high cervical cancer incidence were used to study the ecologic correlation between high-risk HPV prevalence and cervical cancer incidence. The study found that correlation varies with women's age and that high-risk HPV was not able to predict cervical cancer incidence accurately in every country (Maucort-Boulch et al., 2008).

In the case of Cuba, where no national prevalence HPV study had been conducted, the analysis of the age-specific spatial variation of cervical cancer at small area could probably provide useful background information on possible differences in prevalence of HPV high-risk types around the country.

Municipalities with highest smoothed risks of breast cancer were essentially those of Ciudad de La Habana province (urbanisation level of 100%) characterized by a predominantly white population (historically related to socioeconomic status), late age at first birth and low parity (Lorenzo-Luaces et al., 1995). Epidemiological research reveals a positive relationship between breast cancer and socioeconomic factors (Key et al., 2001; Shack et al., 2008). In many cases this can be almost completely explained by such reproductive factors as nulliparity, small number of children, late childbirth, late menopause, and to a lesser degree, diet (Robles et al., 2002).

An interesting finding of the current study is the identification of a small cervix cancer high risk area circumscribed to a few municipalities in the extreme west of the island. However the main determinants of the patterns identified in our study cannot be completely ascertained with the information available on risk factor distribution in the country. Additional epidemiological researches could be necessary in order to obtain more consistent explanations to our results.

It is important to emphasize the possibilities to allow for spatial dependencies in the estimation of relative risks when CAR model is used. Nevertheless, a better fit could probably be obtained if some explanatory variables (in addition to the covariate urbanization level considered here) are able to be included in the model.

On the other hand, it would be particularly attractive and feasible to explore in the setting of an independent study, possible space-time clustering on a larger series of calendar years, following a retrospective approach and using the space-time scan statistics proposed by Kulldorff (1998).

Overall, the present study is the first attempt to introduce in the framework of the NCR of Cuba several statistical techniques involving Bayesian models required for the spatial analyses of cancer risk in small areas. An important advantage of the Bayesian map-smoothing methods applied here is that they greatly reduce the chance of obtaining spuriously high (or low) risk estimates that may falsely indicate disease clustering (Jarup et al., 2002).

In general terms, we consider that this methodology is an essential tool in the determination of cancer control priorities both locally and nationally and we expect to extend their use to forthcoming analysis derived from present results as well as to other important health problems with a high impact on the burden of cancer in Cuba.

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