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Geographical differences in cancer incidence in the Belgian province of Limburg.

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Running head: Geographical differences in cancer.

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ABSTRACT

Geographical differences in cancer incidence in the Belgian province of Limburg.

Background:
Correctly addressing questions of worried citizens with respect to a possible cluster of cancer occurrence requires a risk communication strategy, that is helped by an analytical procedure put in place on beforehand.

Objective:
To construct an approach that would be straightforward, easy to follow by untrained citizens and as robust for both systematic bias and imprecision effects as possible. It should enable a decision about an increased occurrence of cancer, either generally or restricted to specific sites or subgroups, on the level of a municipality or a cluster of municipalities, adjusted for basic characteristics at the same level that are available.

Design:
For all municipalities and most cancers all relevant calculations were performed in tempero non-suspecto and all methods and decision thresholds were defined on beforehand. For each municipality standardised incidence ratios were calculated and smoothed using a Poisson-gamma (PG) and a conditional autoregressive (CAR) model. Clusters were confirmed using the Spatial scan statistic of Kulldorf. Identified clusters were tested for possible confounders using all information that was available on a per municipality level.

Setting and participants:
Limburg Cancer Registry, serving the population of the Belgian province of Limburg (n=781759).

Main results:
We identified a possible cluster of increased prostate cancer incidence (smoothed SIRs around 1.2) and a cluster of increased bladder cancer incidence in males that included seven municipalities with CAR smoothed SIRs between 1.5 and 2.1. SIRs followed a more or less circular decrease around the centre that was situated in Alken and Hasselt, the provincial

capital. Bladder cancer incidence was positively related to an index of socio-economic status per municipality. No relation was found with the other indexes that were available. 82% of all bladder cancers were transitional cell carcinomas (TCC). A repeated analysis based on TCCs only revealed results that were even more outspoken.

Conclusions:
A pre-emptive analysis of possible cancer incidence clustering on a per municipality level proved to be feasible. A cluster of increased incidence of bladder cancer was identified.

INTRODUCTION

At regular intervals somewhere in Europe alarmed citizens or health care workers detect an abnormally high frequency of disease (generally cancer) cases in their region. Environmental causes are easily suggested. Mostly some factory or chimney is available and an etiological hypothesis is built around it. Action groups are formed to demand the removal of the cause, what generally isn't easy and may result in financial claims. It then is to the authorities and the epidemiologists to decide which problems are real and which aren't. Many times the whole process ends in confusion and increasing distrust by citizens in a government that wasn't able to remove or adequately address their worries. Preventing such stories requires a careful risk communication strategy that is helped by an analytical procedure put in place on beforehand. Until recently, such procedure was not available in Belgium, as indeed in a number of other European countries. After being confronted with a number of similar cancer-related episodes in Belgium, the research team of the Limburg Cancer Registry decided to cope with the challenge. We intended to construct an approach that would be straightforward, easy to follow by untrained citizens and as robust for both systematic bias and imprecision effects as possible. It should provide information about an increased incidence of cancer, either generally or restricted to specific sites or subgroups, on the level of a municipality or a cluster of municipalities, adjusted for characteristics at the same level that are available. In case a real increase would be identified, the epidemiological research relating this increase to possible causes, was considered to be a next and separate step with a different approach and outside the expertise or the primary responsibilities of the cancer registry.

When dealing with the issue we had to cope with a number of technical problems (1), such as:

1. The necessary data with respect to disease incidence can be missing or unreliable.
2. Post-hoc data-collection or decisions about the procedures led by prior suspicion of an increased disease incidence hampers the application of most statistical methods.
3. Comparisons between regional groups are subject to ecological fallacy unless both the rate of disease in people that are not exposed to the etiological agent is the same in all populations and the effect of exposure is the same in all populations.
4. In relatively small regions or for regions with relatively low numbers of diseases, disease incidence rates tend to differ largely due to random error and may take misleadingly high or low values.

In this paper we describe the procedures that were developed to deal with these problems and the results of our first analyses.

METHODS

Data collection:

Data were collected in the framework of the Limburg Cancer Registry (2,3) and include 9989 histologically or cytologically confirmed primary invasive cancers that were observed among male and female inhabitants (n = 781759) of the Belgian province of Limburg within the period 1996-1998. For each of the 44 municipalities in Limburg (population averaging 18085 and ranging between 4311 and 67647 with one outlier totalling 86 people) the number of cases of a specific type of cancer was recorded.

The Limburg Cancer Registry.

A detailed description of the procedures and results of the Limburg Cancer Registry (LIKAR) has been published before (2,3). Of all cytological and pathological tests resulting in a cancer diagnosis and related to somebody belonging to the population at risk, patient characteristics, doctor characteristics, and diagnostic results are centrally registered. Data are provided by all pathological laboratories located in the province and all pathological departments outside the province which more than occasionally examine samples from Limburg inhabitants. An unique encrypted code guarantees that all data of the same patient are recognised as such by the registry while it is impossible to identify this individual without consulting the practitioner or the laboratory that provided the data.

Records entering the registry are extensively tested to decide whether or not a record is a new primary tumour, to identify records related to people outside the province of Limburg, as well as non-cancer results, and finally, to be defined as a metastasis, a borderline malignancy or a cytologically or histologically proven primary cancer. There are however, a number of cases where a pathologist has to intervene manually.

All cancers are classified according to the ICDO-2 classification. If two tumours of the same histological type occur simultaneously at the same site (or subsite for tumours of colon, rectum, skin, bone and soft tissue) one tumour is registered (e.g. two adenocarcinomas in the stomach result in one registration). Basal cell carcinomas of the skin and carcinomas in situ of the cervix uteri were excluded from this analysis.

Underestimation happens in very old patients, in whom biopsies are not always performed because of a poor general condition or in some deeply located tumour sites such as brain or pancreas. As haematological cancers are often diagnosed by haematologists and not by

pathologists, also in this field under-registration can be expected. Linking our results with the national Cancer registry and exchanging information between the registries of the Euregio (Belgium, The Netherlands and Germany) provide data on Limburg inhabitants that are not examined by our pathologists' network or that are cared for in nearby Dutch or German centres.

For this analysis histologically or cytologically confirmed cases only were included. The likelihood of false positive diagnoses therefore is expected to be extremely low. Impossible combinations of data are searched using automated test procedures including the IARC check software: illegal codes are not allowed (for example neutral as gender, or a city outside the catchment area) on the level that is reported and a logical consistency between data is necessary (for example: between sex or age and site or type of cancer). Double recording of the same cancer is avoided as all entries are tested with a set of algorithms that were especially developed for this purpose.

Spatial analysis

Age standardisation

The standardised incidence ratio (SIR) for region *i* is obtained from the ratio of the observed and expected number of cases (O_i/E_i) in that region ($i=1,\ldots,n$). Indeed, independently in each area *i*, the number of cases is supposed to follow a Poisson distribution with mean $E_i r_i$, where $r=(r_1,\ldots,r_n)$ are the unknown area-specific relative risks of having the disease. The likelihood of the relative risk is:

$$O_i \mid r_i = \exp[-E_i r_i]\frac{(e_i r_i)^{O_i}}{O_i!}$$

Hence, the maximum likelihood estimate (MLE) of r_i equals O_i/E_i with estimated standard error $s_i=\sqrt{(y_i/E_i)}$. We use the indirect method for standardisation. That is, the expected value E_i is calculated by applying the general age-specific reference rates of Limburg to each municipality. Confidence intervals for the SIRs are calculated using the error factor (4):

$$\exp\left(z_{1-\alpha/2}\sqrt{\frac{1}{O}}\right)$$

Smoothing

The most extreme SIRs are those based on only a few cases. On the contrary, the most extreme p-values of tests comparing SIRs to unity or confidence intervals excluding unity

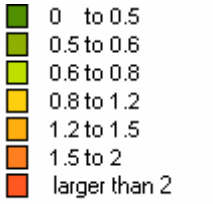
may simply identify areas with large populations. These two drawbacks are emphasised in studies on rare diseases or small areas, making the interpretation of raw SIRs or of p-values difficult or even misleading (1,5).

Actually, for a rare disease and small areas, since individual risks are heterogeneous within each area, the variability of the average risk of the area exceeds that expected from a Poisson distribution. Extra-Poisson variation can be accommodated by allowing relative risks to vary within each area. Bayesian methods can be used for this, giving smoothed estimates of relative risks. Indeed, they smooth SIRs based on unreliable data but preserve those based on large populations. Bayesian estimates of the relative risks are thus easier to interpret.

In this project we considered different methods to identify possible ``high risk" regions. We subsequently used maps of the non-smoothed SIRs, Bayesian methods to map smooth SIRs and the spatial scan statistic of Kulldorff to present our results and to identify high-risk clusters

Carthographic displays

For all maps we used a bi-chromatic range from red to green. The range was based on a log-scale division similar to the suggestion of Knorr-Held (6) and subdivided in 7 categories with a flexion zone in yellow centred around the median:



Bayesian approaches

Bayesian approaches consider, in addition to the observed events in each area, prior information on the variability of disease rates in the overall map. Bayesian estimates of area-specific disease rates integrate the two types of information. They are close to the standardised rates when based upon a large number of events. However, with few events, prior information on the overall map will dominate, thereby shrinking standardised rates towards the overall mean rate. Another advantage of Bayesian methods above the conventional Poisson approach is that the latter does not account for any spatial pattern in disease, i.e. the tendency for geographically close areas to have similar disease rates. Bayesian approaches with prior information on the rates allowing for local geographical

dependence are then pertinent. With this prior information, a Bayesian estimate of the rate in an area is shrunk towards a local mean, according to the rates in the neighbouring areas (5).

Bayesian inference about the unknown relative risks (***r***) is based on the marginal posterior distribution (the product of the likelihood function of the relative risks for the data and a prior distribution of ***r***). In other words, the extra-Poisson variation is incorporated by assuming that the true relative risks follow an *a priori* common statistical distribution on positive values. Several candidate distributions exist, such as the lognormal, Weibull, Gamma, etc. We opted for the conjugate with the Poisson likelihood, the gamma distribution with the so-called hyperparameters alpha and beta and assigning them the following prior distribution: alpha ~ Exponential(1.0) and beta ~ Gamma (0.1, 1.0). This approach has several computational advantages and leads to estimates that have the best robustness properties in the class of all priors having the same mean and variance. Yet, it is not necessarily the most realistic choice. A major drawback with gamma priors lies in the fact that the method does not take into account the geographical location of the region. They do not allow for spatial dependence. Prior knowledge may indicate that geographically close areas tend to have similar relative risks. Breslow and Clayton consider a random-effects Poisson model allowing for over-dispersion and spatial correlation, using the conditional autoregressive (CAR) model of Besag (7). This model can relatively easily be implemented using WINBUGS and has proven effective. For all cancer groups that were studied smooth disease maps have been constructed with both a gamma Poisson and a CAR prior. In this report results are presented for the most frequent cancers.

The spatial scan statistic of Kulldorff

The spatial scan statistic of Kulldorff (8) is defined by imposing a circular window on the map. The base of the window is in turn centred around each of several possible centroids positioned throughout the study region. For each centroid, the radius of the window varies continuously in size from zero to some upper limit. The window is then moved in space so that it visits every possible location. In this way, the circular window is flexible both in location and size. In total, the method creates an infinite number of distinct geographical circles, with different sets of neighbouring municipalities within them, and each being a possible candidate for a cluster.

For each window the number of disease cases inside and outside the window are noted, together with the expected number reflecting the population at risk and relevant covariates.

On the basis of these numbers, the likelihood is calculated for each window. The window with the maximum likelihood, and with more than its expected number of cases, is denoted the most likely cluster. If the window size is allowed to expand until it covers most of the geographic region, the likelihood no longer reflects a cluster of increased disease risk inside the window, but rather a decreased risk outside. Therefore the geographic size of the window was limited to half the expected number of cases (9).

Additional analyses

In case of detection of a cluster of increased cancer incidence, the influence of a standard number of basic characteristics on the incidence is tested by simple linear regression analysis. Dependent variable is the standardised incidence rate per municipality for the identified cancer group. Independent variable is each of the basic characteristics respectively. Basic characteristics are the municipality index of socio-economic status (SES), the index of urbanisation, and the percentage of migrants with a southern-European, eastern European or Islamic (Turkey and the Maghreb countries) nationality. These indexes were provided by the Institute of Social and Economical Geography of the Catholic University of Leuven (Prof. Vanhecke). They are based on data collected in 1991-1999. Additional co-variables can be added according to the specific cancer group under study.

If one of these characteristics proves significantly related to the cancer incidence, the full Bayesian approach is repeated using the relevant characteristic as a co-variable in the analysis.

Procedural and publication policy:

Before the start of the analysis it was decided that crude ratios of cancers per municipality would not be published because of the inherent sensitivity to confounding by age and sex. Age-standardised and sex-stratified SIRs are published. However, SIR differences between municipalities are in itself not considered to be sufficient for the identification of a possible cluster of increased incidence. Poisson-gamma smoothed relative risks and the related displays are available to show possible large scale spatial trends. A cluster of increased incidence is accepted to be identified if CAR smoothed relative risks are found to be larger than 1.5. It is suspected in case of a CAR smoothed relative risk of 1.2 or more.

If a cluster is identified or suspected, the spatial scan statistic is used for confirmation. Next, the relation between basic characteristics per municipality and the incidence rate is examined as described before. If this relationship is found significant, an adjusted Bayesian procedure is

performed. The decision to publish the identification of a disease cluster is eventually based on this analysis.

Clusters that are formally accepted are reported to the population by a carefully prepared press release. Intermediary health care professionals (local GPs, consultants of the relevant disciplines, health care-related authorities of different levels) are informed in detail the days before the press release in order to avoid them being confronted with questions without proper briefing. A telephone number, manned by the provincial health inspector, is made available for people requesting additional information.

RESULTS

Patients and data

During the years 1996 - 1998, 9989 primary cancers were diagnosed and histologically or cytologically proven in inhabitants of the Belgian province of Limburg. 8936 were invasive, 1053 non-invasive tumours. This relates to a crude invasive cancer incidence rate of 440/100 000 person-years for males and 322/100 000 for females. The corresponding standardised rates are 446 and 284 for the European and 303 and 204 for the World standard population.

Spatial analysis

In this section, disease mapping is used as a way of presenting our results and demonstrating the geographical variation of cancer risk in the province.

Figure 1 shows the crude and Poisson-Gamma and CAR smoothed SIRs of invasive cancer in males and females. All three arrays of SIRs are compatible with absence of significant differences in cancer incidence between municipalities. In separate cancer sites major differences between municipalities are found in age-standardized incidence rates. In most cases they disappear after Bayesian smoothing. Figures 2-4 illustrate this with the results for colorectal cancer in both males and females, lung cancer in males and breast cancer in females.

Figure 5 shows the same three types of SIRs for prostate cancer. The Poisson gamma model suggests a gradient with a lower incidence in the east of the province, increasing towards the west. Three non-adjacent municipalities were identified with CAR-smoothed relative risk estimates of 1.2 and 1.3. The presence of a significant cluster was also confirmed by the spatial scan statistic.

Figure 6 shows the results for bladder cancer among males and females. In males a clear geographical cluster of municipalities with an increased incidence was identified. Within this cluster CAR-smoothed SIRs were above 1.5 in all municipalities and reached 2.01 in Alken, the municipality with the highest incidence. Also the spatial scan statistic showed a highly significant cluster ($p=0.0001$). In females similar or higher age-standardised SIRs were found in the same municipalities. These disappeared, however, after smoothing.

The corresponding estimates, together with their confidence intervals can be found in Table 1.

Detailed analysis of the possible prostate cancer cluster

To investigate to which extent the standardized prostate cancer incidence rates within a municipality were influenced by the local PSA screening policy, we related the prostate cancer incidence of each municipality to the PSA screening coverage of all male inhabitants of the municipality with the number of inhabitants as a co-variable, using linear regression. The slope of the regression line was estimated as 443.6 with 95%CI: 158.8-728.3; the Pearson correlation coefficient was calculated as 0.44 (p=0.002). The variation in PSA screening coverage could explain 21% of the total variance of the prostate cancer incidence.

Detailed analysis of the bladder cancer cluster

We related the standardised incidence rates of male bladder cancer of each municipality to an index of the degree of urbanisation (7 ordered categories) by linear regression and found no relation.

Incidence rates were significantly related, however, to a municipality-specific index of socio-economic status (SES). A higher standardised incidence rate of bladder cancer was found in municipalities with a higher SES score (the slope of the linear regression line was estimated as 6.7; 95%CI = 0.8-12.6). This index explained 11% of the variance of the incidence rates. There was no relation between bladder cancer incidence and the per municipality proportion of migrants from the south of Europe, some Islamic states (Turkey and the Maghreb countries) and the Eastern European states.

The proportion of “ever” versus “never” smokers was available for random samples of the population of two cluster municipalities and seven other municipalities. The odds ratio of ever versus never smokers in the cluster municipalities versus the remaining municipalities was 1.48 (95%CI= 0.90-2.44). Using a simple linear regression analysis, there was no relation between the proportion of ever-smokers in these municipalities and the standardised bladder cancer rate.

82 % of all bladder cancers were transitional cell carcinomas (TCC). We therefore repeated the analysis in males for TCC only. The results were basically similar, with the CAR smoothed relative risks tending to be higher in the cluster zone (e.g. 2.34 in Alken). There were now 5 municipalities with a smoothed relative risk above 2.0 and 5 additional municipalities with a smoothed relative risk above 1.5. The TCC cluster identified using the spatial scan statistic was larger than the bladder cancer clusters, but included all municipalities of the initial cluster. Adjusting for the index of socio-economic status while smoothing didn’t change the picture (e.g. CAR smoothed RR for Alken = 2.25).

DISCUSSION

This report shows a way of dealing with the recurrent cluster alarms in a population, that is more or less similar to what has been used in England and Wales (10). Data are both collected and analysed in tempore non suspecto and can be trusted by all parties involved. There is no post-hoc bias. Spurious and misleading results are prevented by Bayesian smoothing, while robust effects are identified. This method also deals with the multiple testing problem. Additional analyses, e.g. for subtypes of cancers are easily performed using exactly the same procedure that has been developed for the main analysis, on condition that the subgroup data are available. If real clusters are detected, an initial epidemiological screening is possible, including the use of municipality-related information. This information can be used either as a co-variable when modelling or as a possible explanation when comparing cluster municipalities with the remaining municipalities of the region. The workload related to the analysis is acceptable if the regional cancer registry has the basic data available. In principle, providing this type of standard analysis is within the possibilities of most cancer registries in the industrialised world. We expected that this procedure could prevent a lot of questions, concerns and mistrust within the population. The results of this study and the reactions to the press release informing the population about the bladder cancer cluster supported this view. Radio, TV and newspapers covered the topic, but did so with all the nuances we wanted them to present. The number of questions during subsequent days was low and could easily be addressed. Contrary to previous occasions in this country, there were no signs of mistrust towards the authorities or researchers.

The results of this study essentially don’t indicate any presence of geographical differences between the occurrence of cancers in municipalities of the Belgian province of Limburg. As usual in this kind of study, major differences are found in age-standardised incidence rates per municipality. They tend to disappear, however, after Bayesian smoothing. There were only two exceptions that deserve a closer look:

Prostate cancer standardised incidence rates were significantly higher in a number of municipalities and the posterior means remained higher in three municipalities after full Bayesian smoothing. The smoothed relative risks were only 1.2 or 1.3, however. Additionally, the three municipalities don’t really cluster geographically. Finally, it is our

view that prostate cancer incidence rates are largely influenced by the PSA screening policy of the local physicians in patients without symptoms. At this moment, these rates may be more informative about health care habits than about cancer incidence. To test this hypothesis, local prostate cancer incidence rates were related to the PSA screening coverage of the male population. As expected a strong and statistically significant relation was identified, with PSA coverage explaining 20% of the variation of incidence rates. For all these reasons we stopped additional analyses with respect to prostate cancer.

Bladder cancer incidence shows a quite different pattern. In males a clear geographical cluster of municipalities with an increased incidence was identified. Fully Bayesian smoothed SIRs reached 2.01 in Alken, the municipality with the highest incidence and were above 1.5 in all municipalities of the cluster. The cluster was confirmed when using the spatial scan statistic of Kulldorff. When focussing on TCCs only, the results were even stronger. In the female population similar or even higher age-standardised SIRs were found in all but one municipalities of the male cluster. These were not significant, however, and disappeared after smoothing, probably as a result of the much lower numbers (n= 63 for females versus 290 for males).

We checked if this result could be explained by weaknesses within our registration process. The ESR of invasive bladder cancer for the whole of the province is 25.7 / 100.000 person-years for males and 4.4 for females. These figures are almost similar to the results of e.g. the Dutch rates. We received the standardised mortality rates per municipality for bladder cancer (P.Hooft) and found no increased cause-specific mortality in our cluster region. However, these numbers are small and the confidence intervals large. Additionally, the input of cause of death for the Belgian mortality statistics is known to be unreliable at this detailed level. We therefore are not prepared to base any conclusions upon them.

Quite some discussion exists among pathologists with respect to coding of invasive and non-invasive papillomas. It is imaginable that one pathological laboratory would classify differently compared to the others. If such laboratory would selectively work more or less for people from the cluster municipalities, this might have a confounding influence on our results. We therefore compared the number of invasive bladder cancers diagnosed by each laboratory in inhabitants of the cluster municipalities to the remaining part of the province and found no difference. We also examined the possible influence of new urologists that recently started working in the cluster region. We therefore identified all urologists working in the cluster region and found seven of them who started their practice between 1989 and 1998. They

were, however, evenly spread over all parts of the province and not more frequently present within the hospitals of the cluster region.
We related the standardised incidence rates of each municipality to an index of the degree of urbanisation by linear regression and found no relation. They were significantly related, however, to a municipality-specific index of socio-economic status (SES). A higher standardised incidence rate of bladder cancer was found in municipalities with a higher SES score, which is unexpected. This score explained 11% of the variance of the incidence rates. One would like to remember, however, that this finding might result from ecological bias. A similar result was found in Finland where cervical cancer incidence rates per municipality were found to be related to the higher SES status per municipality while individuals of high SES status had the lowest cervical cancer incidence (11). Our province is characterised by the presence of a large number of migrants from the south of Europe, some Islamic states (Turkey and the Maghreb countries) and recently the Eastern European states. One could argue that one of these groups may have an increased or decreased risk of bladder cancer compared to the other populations. We therefore also tested the presence of a relation between bladder cancer incidence and the proportion of inhabitants of each of these groups per municipality. We found no relation whatsoever.

In both males and females, bladder cancer has been related to slow acetylation polymorphism (12,13), smoking (13-16) and occupational exposure in the dye, rubber and tyre industry (13-21). Interactions between these exposure factors have also been identified (13-16). We compared the proportion of ever versus never smokers in both groups and found no difference (chi^2, p=0.12). In the cluster region both rubber and asphalt related industries have been active during the last 30 years. If any of these factories can be related to the increased incidence of bladder cancer in the cluster municipalities, either by environmental or by professional influences, can not be decided without an additional full scale epidemiological survey with the individual as the unit of analysis. Actually the main professions in the region are tertiary or farming. In two studies also mining and metal industry have been related to an increased risk of bladder cancer (14,23). Both have been major industries within the province, but outside the cluster region. Although a certain number of cluster region inhabitants may have worked as miners or later as metal industry workers, the proportion will be much lower compared to the remaining part of the province. This can therefore not explain our findings. Summarising, our results support the hypothesis of absence of geographical differences between municipalities with respect to the incidence of cancer, including most cancer sites

separately. For male bladder cancer a clear cluster with an increased incidence was identified. We were not able to explain the presence of the increased incidences by the data that were available to us. All these data, however, were municipality-related. They may therefore be vulnerable to ecological bias and this part of the analysis can only be considered to be of a preliminary nature. Final conclusions about possible explanations can only be based on epidemiological research using a retrospective cohort or case-control design with the individual as the unit of analysis.

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