Author's response to reviews

Title: Municipal mortality due to thyroid cancer in Spain

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Author's response to reviews: see over
Dear sir,

Firstly, we should like to thank you for reconsidering the publication of our study and sending us the comments and suggestions made by a third reviewer. Each of the points raised has now been dealt with below, along with an indication as to which parts of the paper have been amended in line with the respective suggestions.

It goes without saying that we deeply appreciate all the comments and suggestions, in the sure knowledge that these will help improve the manuscript.

1. **Reviewer: Luigino Dal Maso**

   **Major Compulsory Revisions**

   Some additional descriptions of methods could be helpful to the general reader. In particular, the meaning of difference between messages from Figures 1 and 2 should be discussed. Thus, the authors should discuss the degree of smoothing that determines the tradeoff between high sensitivity (truly high-risk areas correctly identified) and high specificity (areas without excess risk correctly identified).

   The description of the smoothing method has been slightly expanded in paragraphs 4 and 5 of the Methods section.

   The meaning of the difference between the messages from Figures 1 and 2 is explained in paragraph 2 of the Discussion section, which is entirely devoted to this aspect.

   The degree of smoothing in the BYM model is determined by the definition of contiguity. In our case, we used the criterion that is most widely used in the literature, i.e., based on the adjacency of the areas:


   **Minor Essential Revisions**

   **Abstract, Background section:**

   A sentence regarding incidence is present while the manuscript referred only mortality. Are the mortality trends for thyroid cancer changing in Spain?

   In the 1990s, mortality due to thyroid cancer in males registered a statistically significant, mean annual increase of 1.21%. In women, however, mortality declined significantly by an average of 0.39% per annum. This comment is reflected in paragraph 1 of the Introduction.


   Your comment has been taken into consideration and the first reference has now been included in the reporting of thyroid cancer prevalence in Spain (paragraph 1 of the Introduction).

   Established risk factors for thyroid cancer are also goiter/adenomas (OR>5 in all studies) and genetic factors, at least for medullary thyroid cancer. Please, correct the sentence and avoid redundant references (older or studies included in meta-analyses).

   As suggested, the sentence appearing at lines 3-4 of paragraph 2 of the Introduction has been suitably rephrased. Similarly, some references related to these risk factors have been eliminated.

   **Methods:**

Our designated aim in this study is to depict the geographic pattern of thyroid cancer, and consequently we are not intent on detecting clusters.

Given the huge difference in incidence and mortality for thyroid cancer in men and women, why are they collapsed? Authors reported no difference (Discussion, page 6) but they should present these results in the two genders.
The spatial pattern of thyroid cancer mortality is practically the same in men and women, and hence we feel that showing two practically identical figures would be redundant. Furthermore, despite the fact that incidence of this tumor is much higher in women than in men, the mortality figures are, nevertheless, very similar. Indeed, this point is made in paragraph 1 of the Discussion section.
Lastly, bearing in mind the low mortality of thyroid cancer, a separate analysis for each sex entails greater problems of statistical power, thus calling for a greater degree of smoothness.

Discussion:

page 7: Association of thyroid cancer and vegetables is weak, if present [ref15], and it may not explain differences in mortality.
In paragraph 5 of the Discussion section, we refer to goitrogenic substances (such as some vegetables) as a possible factor causing goiter, and indeed, as stated in the text, in the opinion of some authors, the role of goitrogenic substances in the etiology of endemic goiter is very limited. In this paragraph, we make no comment on the association between these vegetables and thyroid cancer, and agree with you in claiming that these substances probably do not reflect differences in mortality due to this tumor.

page 8: Association between iodine prophylaxis and thyroid cancer incidence or mortality is debated [VERKOOIJEN HM, et al. 2003 - Cancer Causes Control, 14 13-17.] but the effects seem different for mortality and incidence. Thus, the sentence “…differentiated TC might not have been diagnosed in time and might have evolved into more aggressive forms.” is surprising. Please, provide some reference demonstrating the possibility of “morphological evolution”.
As suggested, this sentence has been appropriately amended (paragraph 6 of the Discussion section).

pages 7, 8, and 9: possible effect of iodine deficiency was discussed in several sentences Please avoid repetitions.
In the Discussion section, we have endeavored to apply the following order: 1) summary of results; 2) study limitations; 3) situation of endemic goiter in Spain; 4) possible factors causing goiter; 5) link between endemic goiter and thyroid cancer; 6) situation in the three highest-risk autonomous regions in our study (Galicia, Asturias and Canary Islands); 7) possible influence of other thyroid cancer risk factors (ionizing radiation and genetic factors); and 8) conclusions. While it is possible that iodine-deficiency-related matters are mentioned under some of the above points, we nevertheless feel that, since goiter is one of the greatest risk factors for thyroid cancer, it is necessary to reflect the situation country-wide as well as in the highest-risk areas.
References:

Please include only more relevant and recent references (e.g.: 1. Update ref 4; delete 8-10, 16,20-22, provide website for ref31) and, if possible reduce the Spanish references hardly available to internationally.

As suggested, the English-language references indicated have been eliminated. However, we feel that the Spanish references are fundamental for the purpose of highlighting possible causes of the excess risk detected in Galicia, Asturias and the Canary Islands. Unfortunately, we do not have any scientific papers in English which reflect the situation that prevailed in these areas some decades ago.

2. Reviewer: Milena Maria Maule

General

The authors use a Bayesian hierarchical model to study the spatial variation of mortality risk for thyroid cancer in Spain. Data are analysed at a small-area (municipality) level. The method used is appropriate for descriptive purposes and provides interesting results. The spatial pattern of mortality for thyroid cancer, given the high survival rates, is not a good indicator of the spatial distribution of the occurrence of thyroid cancer. The authors address this point in the Discussion, where they suggest that mortality could represent incidence of the most aggressive type. Results would perhaps be easier to interpret if the analyses were restricted to the most aggressive cancer type only. This would lower the possibility that geographical differences in the risk of death (especially the high risk in mountainous remote areas) reflect geographical differences in the accessibility to healthcare. However, the selection of a particular histological type may not be possible if the data are extracted from the national death records.

As you rightly say, it would have been extremely interesting to perform the mortality analysis by histological type. However, the possibilities of analysis are limited by data availability, and the two ICD versions used to code underlying cause of death in Spanish mortality registries during the study period do not allow for differentiation by histological type.

Minor Essential Revisions

1) Introduction:

p.3, lines 6-10. To me the sentence “As a consequence of this increased incidence and stable mortality, prevalence attributable to cases diagnosed in the preceding 5 years has increased to a figure of 6632” is not clear. In the previous sentence it was stated that mortality among men showed a statistically significant mean annual increase of 1.21%, and among women a statistically significant decrease of 0.39%. Has mortality resulted stable in the previous decade for both men and women together, or do you mean that it has become similar for the two sexes?

In view of the fact that the sentence to which you refer might lead to confusion, it has now been reworded in the manuscript.

2) Results:

p.6, lines 4-5. In Table 1, 38 towns are listed rather than 39, and 11 provinces rather than 12. It is stated that 75% of towns are in 2 Autonomous Regions, Galicia and Asturias, but in Table 1 19 municipalities correspond to Galicia (50%) and none to Asturias. Maybe I am just missing out something of the administrative borders of the Spanish regions, but could you please clarify?

Indeed, in Table 1 we mistakenly omitted one town and forgot to indicate the towns that belong to the Region of Asturias. These errors have now been corrected.
3. **Reviewer:** Pierre Goovaerts

**Major Compulsory Revisions**

This manuscript presents the application of an existing method (Bayesian MCMC simulation) to the mapping of the standardized mortality ratios and the probability of exceeding a relative risk of one for Thyroid cancer in Spain. It would be useful to incorporate a short description of the method in layman terms so that the reader understands the basic principles of the smoothing method. MCMC has become very fashionable in the health literature but most practitioners tend to use it as a “black-box”, without due attention to the assumptions underlying this methodology. In particular, two critical components of the application of the Bayesian approach are: 1) the specification of the prior probabilities to start the iterative procedure, and 2) the CPU requirements which often makes the approach unpractical. The authors used non-informative priors, which raises the question of the relevance of a Bayesian approach if no prior information is available. I would like this issue to be discussed in the manuscript. Also, the expression “acceptable computation term” on Page 5 is very vague and both the CPU time and characteristics of the computer used for the computation must be specified in the manuscript. I also wonder how sensitive the results are to the use of a different type of contiguity criterion.

1. As prior distributions we chose improper priors. Gamma distribution are commonly assumed in a disease mapping context, as stated in Chapter 6 of Lawson et al's book, which has now been added to our paper's reference list.

2. As stated in paragraph 1 of Results, “an acceptable computation time and conventional computers” were used. A burn-in of 300,000 iterations was used for each model, which entails a computation time of around 18 hours using a conventional computer (2GHz). This point has again been addressed in paragraph 5 of the Methods section.

3. With reference to your comment on the smoothing method, a brief explanation has now been added to paragraph 4 of the Methods section, along with the pertinent formula.

4. The criterion of contiguity chosen is the standard criterion most widely used in the literature, i.e., Ugarte MD, Ibáñez B, Militino AF. Detection of spatial variation in risk when using CAR models for smoothing relative risk. Stoch Environ Res Risk Assess 2005, 19:33-40. In our experience, similar criteria (for instance, towns coming within a circle of a given diameter) yield comparable results. In this context, it thus seems sensible to use the standard criterion.

**Minor Essential Revisions**

The English needs to be improved. For example, the expressions "Spain lies near the middle of the table", "Spain gave an undertaking to eradicate", or "in connection wit this last-mentioned aspect" must be modified.

The paper has been amended as requested.