We would like to thank to the reviewers their useful and comprehensive comments, as they clearly contribute to improve our work. We tried to follow all the recommendations made by the reviewers. Detailed answers to their comments can be found bellow. Additionally, we have highlighted the changes (in yellow) in the manuscript.

**Notas do editor:**

**COMMENT 1:**

**- com o objectivo de optimizar a legibilidade do seu artigo e assim incrementar potencialmente as citações do mesmo, recomendamos que os conteúdos redigidos em inglês sejam revistos por  um "native speaker", tradutor qualificado ou empresa especializada em serviços de "language polishing";**

**REPLY:**

This manuscript was proof-read by the Proof-Reading Services, where it was reviewed by a native English speaker, before being submitted to Acta Medica Portuguesa.

**COMMENT 2**

**- o resumo e o abstract não deverão incluir abreviaturas;**

**REPLY:**

The abbreviations were removed from the Abstract and Resumo section.

**COMMENT 3:**

**- o resumo e o abstract deverão reflectir fielmente a estrutura do artigo, pelo que é necessário que incluam um parágrafo independente relativo ao capítulo "Discussão";**

**REPLY:**

A discussion subtitle was added to the Abstract and Resumo section.

**COMMENT 4;
- no idioma português, as unidades devem ser separadas das casas decimais por vírgulas e não por pontos - estes serão exclusivamente usados nos conteúdos redigidos em inglês;**

**REPLY:**

As per editor’s comment the decimals were identified with commas in the section written in Portuguese.

**COMMENT 5:**

**- no corpo do manuscrito as referências deverão ser assinaladas em sobrescrito (expoente), a seguir a vírgulas (,) e pontos finais (.), ou antes de ponto e vírgula (;) e dois pontos (:);**

**REPLY:**

The references were reformatted to fit the comment above.

**COMMENT 6:**

**- por outro lado, o corpo do manuscrito deverá incluir um capítulo intitulado "Conclusão";**

**REPLY:**

A conclusion section was included in the manuscript (highlighted in yellow).

**COMMENT 7:**

**- as obras consultadas online deverão referir, na listagem final, o nome do documento, bem como o dia, mês e ano do acesso, e ainda o link completo que a elas dá acesso;**

**REPLY:**

The references were corrected in order to meet the editor’s comment.

**COMMENT 8:**

**- as imagens que compõem a Figura 1 não se apresentam em conformidade com as Normas de Publicação da Acta Médica Portuguesa, pelo que os autores deverão proceder ao upload de novas imagens, como documentos suplementares à submissão. Cada ficheiro a carregar deverá conter uma única imagem, correspondendo à imagem ORIGINAL/SOURCE, sem qualquer tipo de edição (não são aceitáveis, nomeadamente, crops/cortes, informação do doente apagada, printscreens, letras ou setas sobre as imagens). Toda e qualquer edição necessária nas imagens será realizada pelo sector gráfico da Acta Médica Portuguesa. Cada imagem deverá ter uma qualidade mínima de 1200 pixeis de largura e altura proporcional.**

**REPLY:**

New figures with the highest resolution possible have been uploaded and should be included in the manuscript side-by-side in the following order: All, < 50 years, 50-64 years, ≤64 years and ≥65 years.

**Revisor A:
Vide documento carregado no portal da Acta Médica Portuguesa.**

**COMMENT 1:**

**A análise de dados efetuada é superficial e encontra-se apresentada de forma bastante ligeira. Não existe qualquer fundamentação relativamente aos procedimentos estatísticos utilizados no trabalho. A importância dos estudos temporais e espaciais deve-se bastante à existência de dependência entre as observações, quer no tempo e/ou no espaço. Assim, quando se trata de analisar dados espaço-temporais, espera-se uma análise que tenha em conta tal dependência.**

**REPLY:**

This study was conducted as a broad and comprehensive study in terms of space and time of breast cancer mortality in Portugal. Also, this study aimed to identify the presence of critical areas in this mortality rate. Therefore, we considered that the descriptive statistics used was adequate methodology that matched the first objective of this study, and that the spatiotemporal analysis was the preferred method for the assessment of the second objective as it has been wildly used in this sort of analysis (<https://www.satscan.org/references.html>).

**COMMENT 2:**

**Estudos Seccionais, Estudos Temporais e Espaciais**

**Foram efetuadas análises descritivas seccionais, utilizando , de forma independente, regiões e tempo. Existindo dados temporais e dados por regiões, é possível descrever a evolução do número de casos ao longo do tempo, por região, ou descrever a distribuição do número de casos por região, ou distrito, num determinado ano. Tal abordagem não se encontra presente neste estudo. Além disso, em estudos meramente descritivos, não é possível aferir a significância estatística dos resultados. Assim, e por exemplo, não é possível admitir como suficiente “Both the older (≥ 65 years) and the younger women (<50 years) showed an increasing trend in the MR (+0.896% and +0.725%/year, respectively) while the middle-aged group (50–64 years) and the ≤ 64 years had a decreasing tendency in the BC mortality in this analysis (-1.781% and -0.0907/year). ‘’ para se poder explicar o que quer que seja, sem apurar a significância dos resultados.**

**REPLY:**

This study was quite comprehensive, therefore the data presented in the main document had to be carefully selected and reduced to the most relevant one values. However, in the supplementary tables further data on the regional mortality rate analysis per year can be found.

We do not fully understand the point of the reviewer in this comment. What does the reviewer exactly mean with “estudos meramente descritivos”? Is it the reviewer referring to the statistical method or the type of study?

**COMMENT 3:**

**Estudo Espaço-Temporal**

**Em termos de análise espaço-temporal, esta reduz-se à utilização do software SaTScan como uma “caixa negra”. O software SaTScan, desenvolvido por Martin Kulldorf, em 1997, incorpora estatísticas de varrimento scan statistics, que permitem efetuar quer estudos descritivos , quer estudos inferenciais na deteção e identificação de clusters no espaço e no espaço-tempo. No âmbito da inferência, havendo vários métodos para a definição de clusters, é importante explicitar o método utilizado no estudo, assim como o modelo considerado baseline. O modelo utilizado não é sequer referido no artigo.**

**REPLY:**

During this study the method used for the spatiotemporal analysis was spatiotemporal scan statistics. This method used circular windows including the maximum of 20% of the population. In view of the reviewer’s comments the following sentence was changed: “The identification of temporal and spatiotemporal clusters plus the detection of spatial variations in temporal trends was conducted using the statiotemporal scan statistics23 using a Poisson model and circular windows circular windows with a maximum of 20% of the studied population.”

------------------------------------------------------

**Revisor B:**

**Breast cancer is the cancer with highest incidence rate in Portugal. Although breast cancer mortality is low, this disease is the leading cause of death among women with cancer. The presented paper is original. It is the first study that characterizes the breast cancer mortality in Portugal, from 2002 to 2013, both from a temporal and spatial point of view. The identified trends and areas in breast cancer mortality identified by this paper can be considered in public health strategies. I have a few comments:**

**COMMENT 1:**

**Why it was study the decade 2002 to 2013, instead of a more recent decade?**

**REPLY:**

At the time of data collection, the 2002-2013 data were the latest years for which the breast cancer number of deaths were available in the INE database. Hence this decade was the selected period for this study. We are aware that currently there are more recent data available (death data is available until the year 2017), however, these were not considered in this study as the statistical analysis was already completed at the time of their publication.

**COMMENT 2:**

**Introduction:**

**a) Last sentence of the first paragraph: It is too long. I suggest to divide in two sentences.
b) Second paragraph, line -4: I am not native speaker, but I think it should be “Both BC and AMR presented fluctuations in time and according…”**

**REPLY**

a) The sentence was changed in order to comply with the reviewer suggestions to: “The BC-MR in Europe and Portugal showed a decline since 1993 until 2010.7 Furthermore, between 2009 and 2011 the Portuguese female BC-AMR was among the lowest in the European Union, with an AMR for women <65 years in the second quintile and an AMR for ≥65 years in the first quintile.9”

b) The sentence was changed in order to be clearer, as per reviewer’s suggestion: “Both BC mortality and AMR presented fluctuations in time and according to the different Portuguese regions under analysis.9,11,13–19”

**COMMENT 3:**

**Methods:**

**a) What is the advantage of considering the age group <= 64 years, when the is information about the age-groups <50 years and 50-64 years?**

**b) I’m not sure if “determined year” is commonly used in English writing.**

**c) Why Azores and Madeira were left behind in the identification of temporal and spatiotemporal clusters?**

**REPLY**

a) The analysis on the ≤64 years group (which englobes the <50 and the 50-64 years age-groups) was conducted because the mortality rate by breast cancer prior to the age of 65 was one health indicator being assessed continuously in our country.14 Additionally, the analysis conducted in this age group done in order to obtain comparability of the published results for breast cancer mortality in the Portuguese setting.9,13–19

b) According to the reviewer’s suggestion the sentence was changed to: “a certain area and in a particular year”.

c) The Azores and Madeira archipelagos’ data were excluded from the temporal and spatiotemporal analysis they do not have a spatial continuity (no neighborhood notion) and they represent specific realities which would not be comparable with the mainland setting.

**COMMENT 4:**

**Results:**

**a) 2nd paragraph, line 2: “(population density)” means “(high population density)”?.**

**b) 2nd paragraph, line 9: Instead of “The elevated MR” believe that it should be “The high MR”.**

**c) 2nd paragraph, last sentence: Pease improve this sentence. What do you mean with “health determinants’ distribution”. When you refer “differences in this area” you are comparing with the mainland?**

**d) 3rd paragraph, line 4: you refer “three areas an periods” but in the rest of the sentence only the areas are reported.**

**e) 5th paragraph, line 4-last: This paragraph starts which a sentence about the limitations of your work. The last sentence, as it is written is not a limitation but just a list of the several factors that could explain the spatial differences detected. Thus, as it is, this sentence makes more sentence in the paragraph where the spatial differences are discussed. Is it possible to include in the spatial analysis variable associated with the factors that you list? If yes, why it was not done?**

**f) 6th paragraph, last sentence: Please improve this sentence.**

**REPLY:**

a) As per reviewer’s suggestion, the sentence was corrected to: “(high population density)”

b) As per reviewer’s suggestion, the sentence was corrected to: “The high MR in the Lisbon region”

c) As per reviewer’s comments, the sentence was changed to: “The fact that Madeira shows the highest BC-AMR might be a consequence of health determinants or health care differences in this area versus the rest of the country.”

d) As per reviewer’s comments the sentence was emended to: “Additionally, three areas and periods were detected as showing a higher or lower MR than the rest of the country: two clusters with a superior MR located in the city of Lisbon (2002-2007, urban, RR: 1.74) and in the Centre (2008-2013, rural, RR: 1.26), plus a cluster in the North that presented an MR below the expected for the area and period (2002-2007, intermediate, RR: 0.54).”

e) The factors listed in this last paragraph were not assessed in the current study due to the inexistence of most of this data (at a county level) in the public domain or in the database used. According to the reviewer’s comments, the sentence was changed to: “Additionally, the spatial differences detected in this health outcome could be attributed to various factors which were not considered in this analysis, such as socio-economics […]”.

f) As per reviewer’s comments the sentence was changed to: “The North region was identified as the area with the lowest MR, prompting further analysis of local strategies and on the protective factors for BC mortality which could potentially be adopted in the critical areas identified in this study.”

------------------------------------------------------
**Revisor C:**

**Methods: Does it describe how the objectives were reached? Are the study design and methodology appropriate to its objectives? Are there any methodological failures? Is the statistical method accurate? Is the methodology in epidemiological based manuscripts adequate? Methods are appropriate for the purpose of the study. A couple of notes to consider:**

**COMMENT 1:**

**It is not clear in the text why the authors considered the age class “<= 64”. It should be clear why the choice of not mutually exclusive age-groups.**

**REPLY:**

The analysis on the ≤64 years group (which englobes the <50 and the 50-64 years age-groups) was conducted because the mortality rate by breast cancer prior to the age of 65 was one health indicator being assessed continuously in our country.14 Additionally, the analysis conducted in this age group done in order to obtain comparability of the published results for breast cancer mortality in the Portuguese setting.9,13–19 Additionally, the Methods section was changed in order to reflect the reviewer’s comments: “not mutually exclusive age-groups (<50 years,4,8,9,33 50–64 years, ≤64 years [for comparability reasons],9,13–19**” .**

**COMMENT 2:**

**The software used should be correctly referenced as IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) not as in the text “Statistical Package for Social Sciences (SPSS™, version 22 for Windows)”**

**REPLY:**

The text was corrected as per the reviewer’s comment to: “The data was analysed using the software IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.)” […].

**COMMENT 3:**

**Discussion: Does it explain the relevance of the results? Does it describe any limitation? Does it describe any areas in need of further study?**

**Since the study only analyses mortality rates, many questions are left unanswered. Nevertheless, the authors make valid discussion of the potential reasons for the results presented. One piece of information that should also be included in the discussion is the lack of a screening program in Lisbon. This may also be an additional factor for the present results.**

**REPLY:**

The breast cancer local screening actions in the south region of Portugal only started in 2002-2005 (A). In 2012, the coverage of the BC screening was residual in the Lisbon area16 whereas the national adhesion rate has ranged between ~60-~70% in 2009-2014.9,13 In 2014, the adhesion rate still showed dissimilarities between Lisbon (29.7-58.9%), and other regions of the country.13

A - Dourado, F., Carreira, H., & Lunet, N. (2013). Mammography use for breast cancer screening in Portugal: results from the 2005/2006 National Health Survey. Eur J Public Health, 23(3), 386–392.

According to the reviewer’s comment, the following sentence was added in the Discussion:

[…] mortality in these areas. Additionally, there was virtually no screening actions for BC in the Lisbon area, which could also account for the increased mortality in this region.16 The fact that Madeira […]

**Revisor D: (Vide também documento anexo.)**

**General comments**

**O artigo poderá ser particularmente relevante no sentido de dar a conhecer o padrão espácio-temporal da taxa de mortalidade por cancro de mama, em Portugal, ao longo de 10 anos. Identificando áreas críticas, pode fornecer assim informação útil para o planeamento e implementação de medidas fundamentais para uma melhor abordagem clínica e de Saúde Pública para este tipo de cancro. Os autores referem esta importância.**

**São feitas referências a estudos semelhantes sobre a incidência do cancro de mama, mas não sobre a taxa de mortalidade por cancro de mama em mulheres portuguesas. Do que pude averiguar será o primeiro estudo que aplica a metodologia de clustering espácio-temporal para a taxa de mortalidade do cancro de mama em Portugal.**

**O título é adequado. É informativo e curto; e reflecte o conteúdo de forma sucinta.**

**O Resumo está bem elaborado e reflecte o conteúdo do manuscrito de forma clara e eficiente.**

**Na introdução, os objectivos são claramente mencionados e é justificada a relevância do estudo.**

**Os métodos utilizados, em particular as técnicas de clustering espácio-temporal estudadas, são adequados para atingir os objectivos definidos. As metodologias estão bem referenciadas e expostas.**

**De um modo geral, a apresentação a análise dos dados está clara e bem elaborada. Apenas a notar que ao confrontar alguns dos valores no texto com os das tabelas não é fácil a sua compreensão (este facto é indicado como nota no manuscrito revisto, em anexo). Este aspecto pode ser melhorado.**

**Na discussão, são explicadas as possíveis razões/implicações dos resultados obtidos. Os autores identificam algumas limitações do estudo e pontos que merecem estudo futuro mais aprofundado. As conclusões são relevantes e vão de encontro ao que foi definido nos objectivos.**

**A lista de referências é adequada. Deve ser feita uma verificação das referências. De um modo geral, estão bem indicadas, no entanto, por exemplo, nas referências 9, 13, 16 e 21, referências online, entre parêntesis rectos aparece “internet” onde deveria aparecer a data da consulta do recurso. Não havendo essa informação, penso que não deve aparecer nada e apenas o endereço online onde está disponível.**

**O manuscrito tem a extensão adequada. E está apresentado de forma clara.**

**Recomendo a publicação do manuscrito na AMP, uma vez que pode trazer um importante contributo para o conhecimento do perfil da taxa de mortalidade por cancro de mama no país, a nível global e local, ao longo dos anos do estudo.**

**Em termos de prioridade de publicação colocaria o manuscrito nos primeiros 20%.**

**REPLY:**

The available information on the mortality rate by breast cancer in Portuguese women is briefly discussed in the introduction section: “(mortality rate [MR] 30.1/100,000 inhabitants,3 age-adjusted MR [AMR] 18.4/100,000 inhabitants2).” Please note that the age-adjusted MR value reported for Portugal was corrected in order to reflect the published value.

The references 1, 3, 9, 13-19, 21, 37 and 38 were amended in order to include the date of consult of the respective webpages (marked in yellow).

**COMMENT 1:**

**Results, Analysis per region section:**

**Não encontrei estes valores na Tabela 1: “15.91 and 18.85/100,000 inhabitants”**

**REPLY:**

The 15.91 and 18.85/100,000 inhabitants rates correspond to the breast cancer adjusted mortality rate for the North and Center regions in the 2002-2013 period. These results can be found in the Supplementary Table 1.

In order to reduce misunderstandings, the indication of Supplementary Table 1 was added to the end of the sentence: “The regions with the lowest AMR were North and Centre (15.91 and 18.85/100,000 inhabitants) (supplementary Table 1).

**COMMENT 2:**

**Results, Spatiotemporal analysis by counties section:**

**?Verificar este valor. A que corresponde? “n=17,767”**

**REPLY:**

17,767 were the number of female breast cancer deaths reported in the Portugal mainland in the period of analysis (2002-2013).

In order to reduce misunderstandings, the sentence containing this information was corrected as per reviewer’s suggestion: “Spatiotemporal analysis by counties (n=278): In the period 2002–2013, the annual female BC-MR in the mainland was 28.4/100,000 inhabitants (n=17,767).

**COMMENT 3:**

**Discussion**

**Se o valor indicado foi calculado pelos autores as referências deveriam vir a seguir a “publications”**

**“[…] were 28.47(3,9,13,15–18) and 19.46/100,000 inhabitants(2,9,13,15–18), respectively, matching previous publications, and placing Portugal […]”**

**REPLY:**

This sentence was corrected in order to reflect the reviewer’s comments: “[…] were 28.47 and 19.46/100,000 inhabitants, respectively, matching previous publications,2,3,9,13,15–18 and placing Portugal […]”