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The use of intervention analysis of the mortality rates from breast cancer in assessing the Brazilian screening programme

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Abstract **Introduction:** There is a need to develop methods to evaluate public health interventions. Therefore, this work proposed an intervention analysis on time series of breast cancer mortality rates to assess the effects of an action of the Brazilian Screening Programme. **Methods:** The analysed series was the monthly female breast cancer mortality rates from January 1996 to March 2016. The intervention was the establishment of the National Information System on Breast Cancer in June 2009. The Box-Tiao approach was used to build a Global Intervention Model (GIM) composed of a component that fits the series without the intervention, and a component that fits the effect with the intervention. The intervention's response time was estimated and used to define the length of the residual series to assess the predictive accuracy of the GIM, which was compared to a one-step-ahead forecasting approach. **Results:** The pre-intervention period was fitted to a SARIMA (0,1,2) (1,1,1)12 model and the intervention's effect to an ARIMA (1,1,0) model. The intervention led to an increase in the mortality rates, and its response time was 24 months. The forecast error (MAPE) for the GIM was 3.14%, and for the one-step-ahead forecast it was 2.15%. **Conclusion:** This work goes one step further in relation to the studies carried out to evaluate the Breast Cancer Screening Programme in Brazil, considering that it was possible to quantify the effects and the response time of the intervention, demonstrating the potential of the proposed method to be used to evaluate health interventions.

Keywords Interrupted time series analysis, National health programs, Mass screening, Breast neoplasms, Mortality rate.

Introduction

Health technology assessment (HTA) has been mainly focused on pharmaceuticals and medical equipment, while HTAs on public health interventions are rarely conducted (Draborg et al., 2005). In 2010, a survey in five countries showed that only five per cent of HTAs were focused on public health (Lavis et al., 2010).

Although randomized controlled trials are considered the standard method for the evaluation of health interventions (Cochrane, 1989), they are not often available in the field of public health as they are usually difficult to conduct (Petticrew et al., 2012). Mathes et al. (2017), reviewed the existing HTA guidelines for this type of technology, and concluded that methods to evaluate public health interventions are not sufficiently developed or have not been adequately evaluated.

This suggests that there is still a need to develop methods and new approaches to evaluate this type of technology. Ramsay et al. (2003) recommended the use of time series regression techniques, especially when randomized controlled trials are not feasible and it is necessary to evaluate changes in a series after an intervention. In this situation, the method of intervention analysis in time series developed by Box and Tiao (1975) seems useful for the assessment of a screening program. A Breast Cancer Screening Programme (BCSP), for instance, has a national scope, making it difficult to carry out a clinical trial. Its effect on the main outcome (mortality from breast cancer) is indirect, which demands monitoring over time. Besides that, a BCSP is also subject to different interventions.

In Brazil, although the screening actions were initiated in 2004 (Brasil, 2004), it became a more structured programme in June 2009, after the establishment of the National Information System on Breast Cancer (SISMAMA in Portuguese) (Brasil, 2008). This intervention promoted the registration of mammography screening procedures and cytopathology-histopathology diagnosis tests, which represented an improvement on the control and evaluation of the actions of the BCSP.

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The BCSP has been evaluated from the perspective of the production of services, coverage, detection rates and access to the target population (Azevedo e Silva et al., 2014; Renck et al., 2014; Ribeiro et al., 2013; Silva and Hortale, 2012). Meanwhile, the series of mortality from breast cancer in Brazil has been mostly studied using a descriptive analysis of its trend, without considering the interventions that occurred over the years (Felix et al., 2011; Freitas-Junior et al., 2012; Girianelli et al., 2014), including the BCSP´s actions.

This work proposed an approach based on intervention analysis on the time series of the Brazilian breast cancer mortality rates to assess the effects of the establishment of the SISMAMA.

Methods

The data of mortality from breast cancer was obtained from the Brazilian Mortality Information System (Brasil, 2015), whose monthly data is available after January of 1996. A time series of female mortality rate from breast cancer was built using the number of monthly deaths and the corresponding monthly female population (Instituto…, 2015), starting in January 1996 and ending in March 2016. All data is publicly available.

For the purposes of the intervention analysis, this series was divided into three periods: pre-intervention from January 1996 to June 2009; post-intervention to build the model from July 2009 to December 2014; and post-intervention to evaluate the model from January 2015 to March 2016.The first two periods were used to fit a General Intervention Model (GIM), which is composed of a pre-intervention model and a model of the intervention effects. The third period was applied to test the predictive accuracy of the GIM. All statistical analysis was done using the *stats* and *forecast* packages of the R Statistical Software, version 2.14.0 (Foundation R, 2015).

Building the Global Intervention Model (GIM)

A Box-Jenkins model was built to fit the pre-intervention period. The parameters of the model were identified through the analysis of the autocorrelation function and the partial autocorrelation function. The Akaike Information Criterion (AIC) and Box-Pierce test were used for the residual analysis of the model. The AIC helps to select the models that minimize the variance of the residuals and the Box-Pierce test verifies if the residuals are random and independent (Box et al., 2015). The most parsimonious model was used to represent the pre-intervention model.

The intervention's effect on the mortality rates was obtained from the difference between the observed data in the second period and the forecast values from the pre-intervention model. This new series, named the residue series, was used to build the intervention effects model applying the Box-Jenkins method.

The GIM results from the sum of the models from the pre-intervention and the intervention effects (that equals zero before the intervention), were as follows:

$$GIM = M_{\,pre\text{-}intervention} + M_{\,intervention\ effects} \tag{1}$$

where each model could be written as the general polynomial form of a SARIMA model:

$$X_t = \left[\frac{\theta_q(B)\theta_Q\left(B^s\right)}{\varnothing_p(B)\varnothing_P\left(B^s\right)\nabla^d\nabla_s^D}\alpha_t \right] \tag{2}$$

where B is a backward shift operator, defined as $\left(B^k Y_t = Y_{t-k}\right)$; where $\varnothing_p(B)$ and $\varnothing_P\left(B^s\right)$ are the autoregressive and seasonal autoregressive terms, respectively; $\theta_q(B)$ and $\theta_Q\left(B^s\right)$ are the moving average and seasonal moving average terms; ∇^d is the backward difference operator, defined as $\nabla^d = (1-B)^d$; ∇_s^D is the seasonal backward difference operator, defined as $\nabla_s^D = \left(1-B^s\right)^D$; and α_t represents the random errors.

Analysis of the intervention's response time

The response time is the length of time from the beginning of the intervention until the point where the maximum level of response due to the intervention is reached. This time represents the period when most changes occur.

To obtain the intervention's response time, the residual series was divided into 11 segments with lengths of multiples of six months, varying from 6 up to 66 months. For each of these segments, the GIM was used to estimate the mortality rates in the post-intervention period. The MAPE was calculated to assess the fitting of each estimation. These values were plotted sequentially considering the segments' lengths, and the point that presents an abrupt fall was considered as the response time.

Analysis of the predictive accuracy of the GIM

A multi-step-ahead forecasting approach and the segments of the residue series with the lowest MAPEs were used by the GIM to forecast the mortality rates from January 2015 to March 2016. These results were compared with the observed values during this period and the estimates using a one-step-ahead forecasting approach, which is an iterative process that uses the pre-intervention model and the observed data to predict one value at a time, providing results with high accuracy (Box et al., 2015). The MAPE was used to measure the predictions' accuracies.

Results

The time series of mortality rate from breast cancer was composed of 243 observations. It showed an increasing trend since the beginning of its recording, with the lowest rate being 0.67 deaths per 100,000 women (recorded in September 1996), and the highest rate being 1.30 deaths per 100,000 women (recorded in March 2016).

The model that best fits the pre-intervention period was a SARIMA (0,1,2)(1,1,1)12. The residual analysis confirmed that this model had the lowest AIC (548.01) and a p-value (0.94) for the Box-Pierce test.

Figure 1 shows the forecast values of the post-intervention period using the pre-intervention model and the observed mortality rates for this period. The forecast series (dashed line) shows a growth at a pace slower than the observed data (solid grey line). This suggested that the intervention had led to an increase in the mortality rate. The intervention effect model was fitted using the residual series and the result was an ARIMA (1,1,0).

The resulting GIM is composed of the pre-intervention model SARIMA (0,1,2)(1,1,1)12 plus the intervention effect model ARIMA (1,1,0), whose polynomial form is shown in Equation 3:

$$GIM = \left[\frac{\left(1+0.9B-0.02B^2\right)\left(1+B^{12}\right)\alpha_t}{\left(1-B\right)\left(1-B^{12}\right)\left(1+0.12B^{12}\right)}\right] + \left[\frac{\alpha_t}{\left(1-B\right)\left(1+0.8B\right)}\right] \quad (3)$$

Figure 2 shows the MAPE values of the post-intervention periods that were estimated using the GIM (Equation 3) and the 11 segments of the residual series. Note that the lowest MAPE were calculated using lengths of 24, 54 and 66 months, but the abrupt fall of the MAPEs occurs when using the segment of 24 months, which is the intervention response time.

Table 1 shows the MAPEs calculated for the forecast series from January 2015 to March 2016. The lowest forecast error (MAPE of 2.15) was obtained using the one-step-ahead approach, and the second lowest (MAPE of 3.14) was obtained by means of the multi-step-ahead approach with the GIM using 24 months of residues, which corresponds to the intervention response time. Figure 3 compares the observed mortality rates and the forecast series using these two approaches. Note that both predictions follow the same pattern for almost one year.

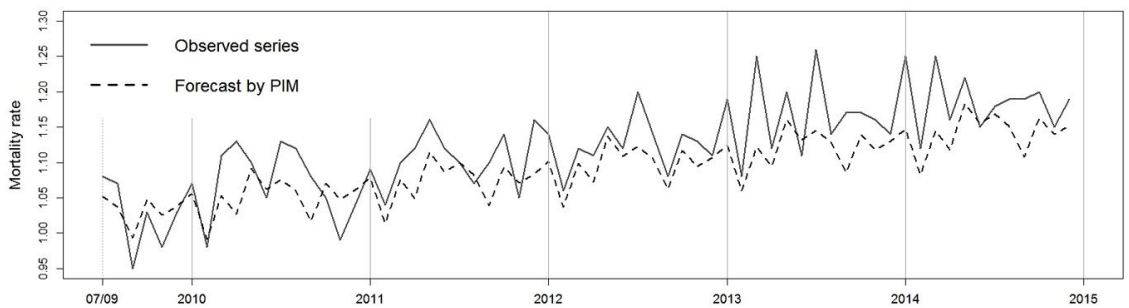

Figure 1. The post-intervention mortality rate of breast cancer in Brazil and the forecast series by the pre-intervention model (PIM).

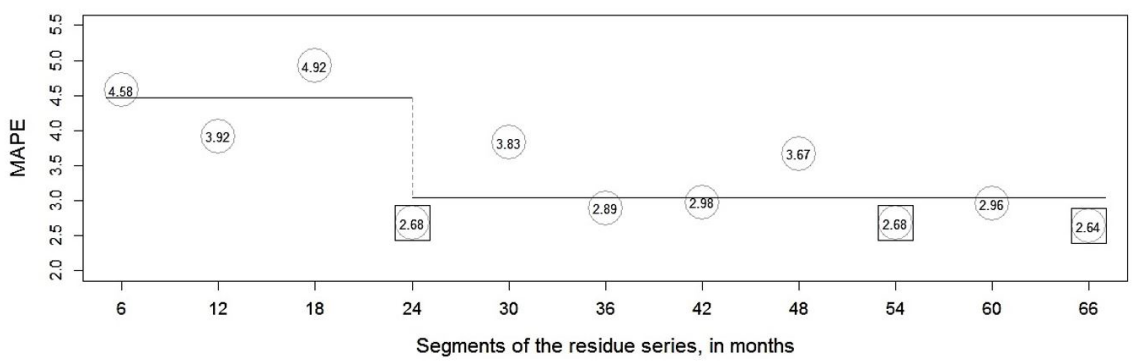

Figure 2. MAPE values of the post-intervention periods estimated by GIM and the segments of residues.

Table 1. Mean absolute percentage errors for the forecast series from Jan/2015 to Mar/2016.

Forecast approach	Model	MAPE
multi-step-ahead	GIM using 24 months of residues	3.14
	GIM using 54 months of residues	3.88
	GIM using 66 months of residues	3.54
one-step-ahead	pre-intervention model using observed data	2.15

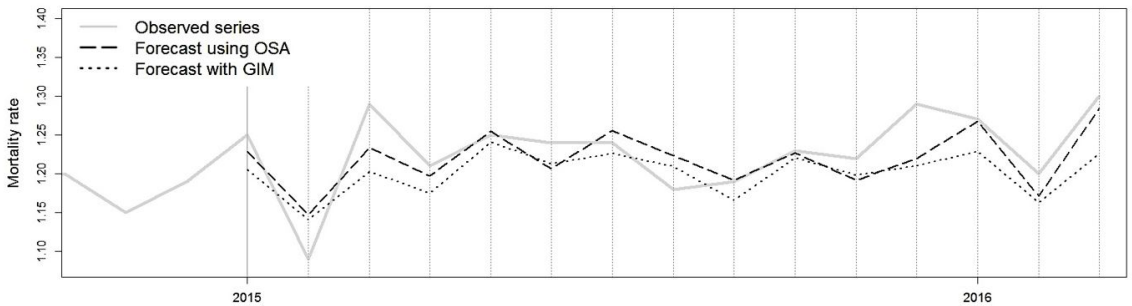

Figure 3. The post-intervention mortality rate of breast cancer in Brazil and the forecast series using the GIM and the one-step-ahead approach, January 2015 to March 2016.

Discussion

The objective of this study was achieved, since the proposed method of intervention analysis detected that the mortality rate series moved away from its course after the establishment of SISMAMA. This deviation revealed a growth in the series rather than a reduction in the mortality rate, which seems somewhat contradictory to the objective of a BCSP (World…, 2012). This finding was somehow expected, taking into consideration that the reduction of mortality is a medium to long term effect of the Programme, and the post-intervention period corresponds to the first five years of the organization of the BCSP. Silva and Hortale (2012) have noted that the reduction of mortality will not be perceived in the initial phase of a BCSP. On the contrary, it is expected that in the initial phase there would be an increase in the identification of new cases of cancer especially among women screened for the first time (Malmgren et al., 2012). These women are at higher risk of being diagnosed in advanced stages, which could result in an increase in the number of deaths registered from this cause (Hofvind et al., 2004; Paci et al., 2004). In Brazil, this situation was already confirmed by Barreto et al. (2012), who suggested that the increased mortality rates could be related to the considerable amount of cases diagnosed in advanced stages of cancer. In the same way, Rezende et al. (2009) observed that 51% of all breast cancers diagnosed in Rio de Janeiro were in advanced stages of the disease (clinical stages II, III and IV).

Additionally, the intervention, i.e. SISMAMA, offers an improvement in the registration of the population with cancer, which can increase the possibility of following up the pathway of these women during the treatment and even the registration of death.

Considering the Box-Tiao method, it was possible to build the GIM that helped characterize the intervention's effect in the mortality rates. That is, the GIM identified and quantified the changes in the series after the establishment of the SISMAMA. It also permitted the estimation of the intervention's response time as 24 months, which is a useful indicator to compare the effects of the intervention in different scenarios. It should be clarified that after this period the mortality rates continued increasing, but this suggests that most of the changes due to the intervention occurred. In this sense, this study overcomes the limitations of using short time series and small post-intervention periods to evaluate public health interventions, as have been pointed out in the literature (Ramsay et al., 2003).

Furthermore, it was shown that the GIM's prediction was improved using the residual series with a length equal to the intervention's response time. The accuracy of this forecast was close to that estimated by the one-step-ahead approach for the period from January 2015 to March 2016, which is an adequate period for planning in healthcare. Nevertheless, the GIM also has an advantage over the OAS approach in forecasting mid- and long-term periods.

Due to the complexity of the BCSP, it is recommended that further studies would include the effects of other interventions in the model, which is possible using the proposed approach. This work is limited to the analysis of one intervention since the main objective was to evaluate a public health intervention implemented on a large scale in the country. Besides that, the proposed

approach could also be applied to characterize the effects of the intervention in different scenarios.

Finally, the approach of this study goes one step further in relation to the previous studies carried out to evaluate the BCSP in Brazil, considering that it allowed to quantify the effects and the response time of the intervention. This makes it possible to compare different scenarios inside the country.

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References

Azevedo e Silva G, Bustamante-Teixeira MT, Aquino EM, Tomazelli JG, Santos-Silva I. Access to early breast cancer diagnosis in the Brazilian Unified National Health System: an analysis of data from the Health Information System. Cad Saude Publica. 2014; 30(7):1537-50. PMid:25166949.

Barreto AS, Mendes MF, Thuler LS. Evaluation of a strategy adopted to expand adherence to breast cancer screening in Brazilian Northeast. Rev Bras Ginecol Obstet. 2012; 34(2):86-91. http://dx.doi.org/10.1590/S0100-72032012000200008. PMid:22437768.

Box G, Jenkins G, Reinsel G, Ljung G. Time series analysis: forecasting and control. 5th ed. New Jersey, USA: John Wiley and Sons Inc.; 2015.

Box GE, Tiao G. Intervention analysis with applications to economic and environmental problems. J Am Stat Assoc. 1975; 70(349):70-9. http://dx.doi.org/10.1080/01621459.1975.10480264.

Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância. Controle do Câncer de Mama: documento de consenso. 1st ed. Rio de Janeiro: INCA; 2004.

Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Portaria SAS/MS Nº 779 de 31 de dezembro de 2008. Define o Sistema de Informação do Controle do Câncer de Mama (SISMAMA). Diário Oficial da República Federativa do Brasil, Brasília, jan. 2008. [cited 2016 November 8]. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/sas/2008/prt0779_31_12_2008.html.

Brasil. Ministério Saúde. Departamento de Informática do SUS. Sistema de Informação sobre Mortalidade. Informações de Saúde (TABNET). Estatísticas Vitais [internet]. Brasília: DATASUS; 2015. [cited 2016 April 13]. Available from: http://www2.datasus.gov.br/DATASUS/index.php?area=0205&VObj=.

Cochrane AL. Archie Cochrane in his own words: Selections arranged from his 1972 introduction to "effectiveness and efficiency: Random reflections on the health services.". Control Clin Trials. 1989; 10(4):428-33. http://dx.doi.org/10.1016/0197-2456(89)90008-1. PMid:2691208.

Draborg E, Gyrd-Hansen D, Bo Poulsen P, Horder M. International comparison of the definition and the practical application of health technology assessment. Int J Technol Assess Health Care. 2005; 21(1):89-95. http://dx.doi.org/10.1017/S0266462305050117. PMid:15736519.

Felix JD, Castro DS, Amorim MH, Zandonade E. Breast cancer mortality trends among women in the state of Espirito Santo Between 1980 and 2007. Rev Bras Cancerol. 2011; 57:159-66.

Foundation R. The R Project for Statistical Computing. 2015. [cited 2016 April 12]. Available from: https://www.r-project.org/.

Freitas-Junior R, Gonzaga CM, Freitas NM, Martins E, Dardes RC. Disparities in female breast cancer mortality rates in Brazil between 1980 and 2009. Clinics. 2012; 67(7):731-7. http://dx.doi.org/10.6061/clinics/2012(07)05. PMid:22892915.

Girianelli VR, Gamarra CJ, Azevedo e Silva G. Disparities in cervical and breast cancer mortality in Brazil. Rev Saude Publica. 2014; 48(3):459-67. http://dx.doi.org/10.1590/S0034-8910.2014048005214. PMid:25119941.

Hofvind S, Wang H, Thoresen S. Do the results of the process indicators in the Norwegian Breast Cancer Screening Program predict future mortality reduction from breast cancer? Acta Oncol. 2004; 43(5):467-73. http://dx.doi.org/10.1080/02841860410034315. PMid:15360051.

Instituto Brasileiro de Geografia e Estatística. [internet]. Brasília: IBGE; 2015. [cited 2016 April 12]. Available from: http://www.ibge.gov.br/home/

Lavis JN, Wilson MG, Grimshaw JM, Haynes RB, Ouimet M, Raina P, Gruen RL, Graham ID. Supporting the use of health technology assessments in policy making about health systems. Int J Technol Assess Health Care. 2010; 26(4):405-14. http://dx.doi.org/10.1017/S026646231000108X. PMid:20923592.

Malmgren JA, Parikh J, Atwood MK, Kaplan HG. Impact of mammography detection on the course of breast cancer in women aged 40–49 years. Radiology. 2012; 262(3):797-806. http://dx.doi.org/10.1148/radiol.11111734. PMid:22357883.

Mathes T, Antoine S-L, Prengel P, Bühn S, Polus S, Pieper D. Health technology assessment of public health interventions: A synthesis of methodological guidance. Int J Technol Assess Health Care. 2017; 33(2):135-46. http://dx.doi.org/10.1017/S0266462317000228. PMid:28434414.

Paci E, Warwick J, Falini P, Duffy SW. Overdiagnosis in screening: is the increase in breast cancer incidence rates a cause for concern? J Med Screen. 2004; 11(1):23-7. PMid:15006110.

Petticrew M, Chalabi Z, Jones DR. To RCT or not to RCT: deciding when 'more evidence is needed' for public health policy and practice. J Epidemiol Community Health. 2012; 66(5):391-6. http://dx.doi.org/10.1136/jech.2010.116483. PMid:21652521.

Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: Lessons from two systematic reviews of behavior change strategies. Int J Technol Assess Health Care. 2003; 19(4):613-23. http://dx.doi.org/10.1017/S0266462303000576. PMid:15095767.

Renck DV, Barros F, Domingues MR, Gonzalez MC, Sclowitz ML, Caputo EL, Gomes LM. Equity in access to breast cancer screening in a mobile mammography program in southern Rio Grande do Sul State, Brazil. Cad Saude Publica. 2014; 30(1):88-96. http://dx.doi.org/10.1590/0102-311X00017113. PMid:24627016.

Rezende MCR, Koch HA, Figueiredo JA, Thuler LCS. Factors leading to delay in obtaining definitive diagnosis of suspicious lesions for breast cancer in a dedicated health unit in Rio de Janeiro. Rev Bras Ginecol Obstet. 2009; 31(2):75-81. PMid:19407912.

Ribeiro RA, Caleffi M, Polanczyk CA. Cost-effectiveness of an organized breast cancer screening program in Southern Brazil. Cad Saude Publica. 2013; 29(1 Suppl):S131-45. http://dx.doi.org/10.1590/0102-311X00005213. PMid:25402242.

Silva RCF, Hortale VA. Breast cancer screening in Brazil: Who, how and why? Rev Bras Cancerol. 2012; 58:67-71.

World Health Organization. World Health Organ Programme Proj Cancer. Breast cancer: Prevention and control [internet]. Geneva: WHO; 2012. [cited 2016 April 12]. Available from: http://www.who.int/cancer/detection/breastcancer/en/.