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The effect of redistribution of ill-defined causes of death on the mortality rate of breast cancer in Brazil

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Abstract *The relevance of breast cancer for women has driven research about mortality of this disease. However, these studies are affected by problems generated by deaths due to ill-defined causes (IDC). To highlight distortions caused by IDC in studies that evaluate mortality, we calculated the age-standardized mortality rates of breast cancer, with and without adjustment for IDC for the years 1990, 2000, and 2010. Then, panel data regression models were estimated and enabled us to identify that the adjustment for IDC: has elevated breast cancer mortality rate of Brazilian municipalities by 9% in the period considered; has drawn mortality rates of the South, Southeast, Northeast and North regions closer; has reduced the increasing trend of mortality by almost 60%, mainly in the Southeast and South regions; has increased, more sharply, the mortality in cities with less than 5 thousand inhabitants; has curbed the significance of most factors associated with breast cancer; has revealed that the effect of longevity and the public health expenditure may be overestimated. These results highlight the importance of adjustment for IDC in producing reliable mortality indicators.*

Key words *Breast neoplasms, Cause of death, Mortality, Statistical models*

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Introduction

Breast cancer is the one that most affects the female audience and is responsible for approximately 25% of cancers diagnosed in women in the world[1] and 21% of tumors (except non-melanoma skin) in Brazil in 2014[2]. Several authors have devoted efforts in order to understand the factors that may affect the mortality rate of this disease[3-20]. However, any analysis of mortality is subject to issues arising from the high proportion of deaths from ill-defined causes (when the underlying cause of death is not well established)[21].

Although deaths from ill-defined causes (IDC) have declined in recent decades in Brazil (indicating improved quality of information recorded in the Mortality Information System - SIM), shortcomings are still found, especially in the North and Northeast regions[19,22]. In 2000, deaths from IDC averaged 14.3% of the country's total deaths, with rates ranging from 6.3% in the South to 28.4% in the Northeast[23].

Since part of these IDC-related deaths can be attributed to breast neoplasms (as revealed by Laurenti et al.[24], after reviewing various death certificates), studies on breast cancer mortality without adjustment for IDC are likely to be subjected to regional bias[25], compromising reliable analyses and restricting studies on mortality to large cities or areas with a better socioeconomic level, where there are fewer deaths from IDC.

The most commonly used method among the techniques used to correct the distortions caused by ill-defined deaths and adopted by the World Health Organization (WHO) presupposes the proportional redistribution of ill-defined causes, considering the same distribution of known natural causes[19,26]. Such procedure has been used in Brazil to correct distortions associated with the mortality of chronic noncommunicable diseases[27] and some specific types of cancer, such as colorectal, stomach, prostate, esophagus[19], cervix[10,19,28], lung[19,29] and breast[10,19] cancers.

Although this technique does not explain the real cause of death[21,30], and its proposal of arbitrary redistribution of ill-defined deaths may artificially inflate mortality rates[19], it would not be feasible to use an "information retrieval" approach (consisting of visiting relatives, hospitals, forensic medicine institutes and health facilities in order to define the real cause of death)[30] when we aim to analyze breast cancer mortality in several Brazilian locations.

Therefore, the technique adopted by the WHO was used in this research to understand how adjustment for IDC would affect breast cancer mortality in Brazilian municipalities and its relationship with the factors associated with the disease.

Overall, the literature recognizes that breast cancer mortality may be associated with socioeconomic, demographic and access to preventive measures factors. Also, it varies according to the region and the period analyzed[31].

In Brazil, we found a positive association of the income level with risk, incidence[32] and breast cancer mortality[33,34]. In fact, due to exposure to environmental factors (i.e., chemicals, physical and biological), the industrialization process itself could increase the risk associated with the disease[25].

Reduced birth and fertility rates and increased life expectancy of the world population have also contributed to growing rates of incidence and mortality of chronic noncommunicable diseases, such as breast cancer[10,14].

Furthermore, studies suggest that higher levels of schooling could reduce the risk associated with breast cancer[32], increase survival and facilitate treatment and early detection of the disease, contributing to reduced mortality[2,16,35].

On the other hand, low availability and poor distribution of physical and human resources hamper the treatment and prognosis of the disease, especially in smaller locations far from capitals, generating overload in reference cancer centers concentrated in large places[36,37].

The factors associated with breast cancer mentioned in this section served as a basis for the elaboration of Equation 3, shown in the following section. From this equation, regression models were estimated, with panel data, which allowed us to identify some distortions due to death from ill-defined causes (IDC) on breast cancer mortality in Brazilian municipalities.

Methods and database

This is an ecological study with Brazilian municipalities used as units of analysis and that considered the mean age-standardized rates of breast cancer mortality focused on the 1990s (1987-1993 mean), 2000 (1997-2003 mean) and 2010 (2007-2013 mean).

Data of this research were clustered in a balanced panel, where the same cross-sectional unit (in this case, the Brazilian municipalities) was analyzed over time, i.e., 1990, 2000 and 2010. This option allowed us to consider more observations

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(improving asymptotic properties of estimators – more robust *t* and F statistics), control unobserved time-constant factors, c_i (*e.g.*, culture, climate, relief, etc.) and conduct dynamic analyses (*e.g.*, trend analysis)[38].

In the context of panel data, a Pooled Ordinary Least Squares (POLS) model is generally estimated using the Breusch-Pagan test[39] to check for any unobserved effects (c_i) affecting the results. In this case, the null hypothesis is: H_0: (σ_c^2) = 0, where σ_c^2 is the variance of the unobserved effect (c). If H_0 prevails, the POLS model is the most appropriate. Otherwise, if $\sigma_c^2 \neq 0$, Fixed Effects (FE) and Random Effects (RE) models are estimated, using Hausman's test[40] to define the most appropriate. This test checks whether the explanatory variables (X_{it}) are correlated with c_i, where H_0: $E[(c_i \mid X_{it}) = 0]$. If H_0 is true, FE and RE will be consistent, however, RE will be more efficient. Otherwise, the Breusch-Pagan test becomes unnecessary and only FE will be consistent[41].

Stata software was used in the descriptive analysis of the variables and the estimates made in this work.

Database

We used female deaths from malignant breast neoplasms in the Brazilian municipalities (reference: residence of the deceased), disaggregated by age group of the Pan American Health Organization (PAHO) and provided by the Mortality Information System (SIM) of the Department of Informatics of the Unified Health System (SUS-DATASUS) (International Classification of Diseases – "ICD-9: code 174", until 1995, and "ICD-10: code C50" after 1995)[42].

To minimize the non-existence of breast cancer death records in some municipalities, we adopted the mean accumulated deaths between 1987-1993 (ICD-9), 1997-2003 (ICD-10) and 2007-2013 (ICD-10), focusing on 1990, 2000 and 2010, respectively. These means were used in the calculation of the ill-defined causes (IDC) adjustment.

Since IDC-related deaths can compromise the reliable analysis of mortality statistics, we used an adjustment procedure suggested by the WHO[26], which presupposes proportional redistribution of IDCs, taking into account the same distribution of known natural causes. This procedure consists in calculating the "percentage of adjustment for ill-defined causes" (PAIDC) for each municipality "i" in the period "t" and its respective "correction factor" (CF), as described in Equations 1 and 2.

$$PAIDC_{it} = \frac{(totalfemaledeaths_{it} - externalcausesdeaths_{it})}{[(totalfemaledeaths_{it} - externalcausesdeaths_{it}) - illdefined\ deaths_{it}]} \quad (1)$$

$$CF_{it} = 1 + \left(\frac{PAIDC_{it} - 1}{2}\right) \quad (2)$$

Once this is done, we multiply the correction factor (CF_{it}) of each municipality "i", in the "t" period, by the total number of deaths, according to the age group, of this municipality in the "t" period. Thus, we obtain deaths adjusted for IDC, which allowed the calculation of breast cancer mortality rates (BCM_{it}), age-specific and IDC-adjusted. Therefore, BCM_{it} corresponds to the mean number of deaths, adjusted for IDC of each municipality in the periods mentioned, divided by their respective population (calculated by the Brazilian Institute of Geography and Statistics - IBGE and facilitated by the Institute of Applied Economic Research - IPEADATA)[43].

Female deaths of Chapter XVI of ICD-9 (*i.e.*, "Signs, symptoms and ill-defined conditions") were used for the period 1987-1993 to set deaths from IDC (Equations 1 and 2). For 1997-2013, female deaths from ICD-10 Chapter XVIII (*i.e.* "Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified") were considered. Total deaths from IDC and external causes are provided by the SIM through DATASUS and were disaggregated by PAHO age group.

Mortality rates adjusted for IDC were standardized by age group with the direct method, using the standard world population stratified by age group[44].

Considering the factors associated with the disease, we can infer that the mortality rate due to breast cancer (BCM_{it}) can be affected by the following variables:

$$BCM_{it} = f\ [HDIE_{it}, HDIL_{it}, HDII_{it}, IND_{it}, FER_{it}, YWC_{it}, \left(\frac{RP_{it}}{UP_{it}}\right), PHE_{it}, NHF_{it}, NHP_{it}, PSD_i, GD_i, TREND_t\ ] \quad (3)$$

Where: BCM_{it} represents the breast cancer mortality rate of municipality "i" in the "t" period (where t = 1990, 2000, 2010).

The remaining variables of Equation 3 were obtained as follows:

Municipal Human Development Index for education (HDIE), longevity (HDILnd income

(HDII) were derived from the United Nations Development Program's Human Development Atlas (UNDP)[45], as well as the fertility rate (FER), the percentage of young women (under 18 years of age) with children (YWC) and the proportion of the rural population in relation to the urban population (RP/UPRP/UP).

To capture the effect of industrialization (IND), we used the Municipal GDP *per capita* of industry (value added at basic prices), calculated by IBGE and converted to constant 2000 values based on IPEADATA's Broad Consumer Index Price, entitled IPCA[43]. Public health expenditure *per capita* (PHE) is provided by the National Treasury Secretariat. Both, IND and PHP are available from IPEADATA[43].

The number of health facilities (NHF) and the number of health professionals with higher education (NHP) in each municipality, both measured per 100 thousand inhabitants, are available in the TabNet program in the DATASUS "care network" module[42]. Data from the Health Medical Care Survey (*Pesquisa Assistência Médico Sanitária* - AMS) for 1992 and 1999 were used for 1991 and 2000. Data for 2010 were retrieved from the National Register of Health Establishments (*Cadastro Nacional de Estabelecimentos de Saúde* - CNES).

Geographic *dummies* (GD) were created for the municipalities of the South, Midwest, Northeast and North (in this case, Southeast is treated as a reference) to compare the municipalities of different regions. Finally, population-sized *dummies* (PSD) were created. Therefore, the "i" municipalities were subdivided into: i) $i < 5$; ii) $5 \leq i < 10$; iii) $10 \leq i < 20$; iv) $20 \leq i < 50$; v) $50 \leq i < 100$; vi) $100 \leq i < 500$; vii) $500 \leq i < 1000$; viii) $i \geq 1000$, where the values represent thousands of inhabitants. In this case, cities with less than 5 thousand inhabitants ($i < 5$) would be the references. The value of the trend variable (TREND) is equal to 1 (in 1990), 2 (in 2000) and 3 (in 2010).

To compare the effect caused by "ill-defined causes" associated with breast cancer, mortality rates standardized by age group (via direct method), with and without adjustment for ill-defined causes, from now on referred to as BCM_{it}^{wa} and BCM_{it}^{un}, respectively. Thus, *wa* indicates "with adjustment" for ill-defined causes, while *un* refers to the "unadjusted" rate.

Due to the period and the unit of analysis used (municipalities), factors such as the age of menarche and menopause, diet type, the percentage of smokers, among others, could not be included in the models. We chose not to use skin color because of the high rate of missing data and the frequent classification errors associated with this variable[46]. Also, since DATASUS[42] began to disclose the number of mammographs per municipality only in 1999, this variable was disregarded.

The excessive correlation between the explanatory variables (Equation 3) could generate multicollinearity, compromising the estimates. However, the "vector inflation factor" (VIF) test, which measures how much each explanatory variable "k" is associated with the others, did not indicate the presence of this problem. Formally: $VIF = 1/(1 - R_k^2)$, where R_k^2 is the traditional R^2 from the estimation of the "k" variable against the other explanatory variables[47].

Results

The descriptive analysis of the variables revealed that the breast cancer mortality rate in Brazilian municipalities, standardized by age group and without adjustment for ill-defined causes (BCM^{un}) was, on average, equal to 8.86 per 100 thousand during the analyzed period (means of 1990, 2000 and 2010), while the mean adjusted mortality rate (BCM^{wa}) was 9.66. Therefore, adjustment for ill-defined causes ended up raising the overall mortality rate by slightly more than 9% (Table 1).

The cross-sectional data analysis revealed that the problem caused by ill-defined deaths showed a reduction in the period considered. In 1990, 2000 and 2010, the adjustment increased the mortality rate by approximately 13.2%, 9.5% and 4.8%, respectively.

Regarding the other variables, there was an increase in the *HDII, HDIL, HDIE*. Meanwhile, the industrial production *per capita* municipal (*IND*) was equivalent to 1,254.14 Brazilian Reals. The fertility rate (*FER*) decreased from 3.20 in 1990 to 1.99 in 2010. The period mean was 2.59 children per woman. On the other hand, the percentage of young women with children (*YWC*) has grown. On average, approximately 2.8% of women under the age of 18 have children. The coefficient (less than 1) associated with RP/UP indicated that most people live in urban areas.

Annual public health expenditure (*PHE*), measured in Brazilian Reals (R$) in 2000, was equivalent to R$ 101.30 *per capita* for the period. The number of health professionals with higher education (*NHP*) and health facilities (*NHF*) was approximately 337/100 thousand inhabitants and 45/100 thousand inhabitants, respectively.

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Table 1. Description of the main variables associated with breast cancer mortality. Brazil, 1990-2010.

Dependent Variable								
	1990		2000		2010		Panel	
	(a)MCM^{SC}	(b)MCM^{CC}	(a) MCM^{SC}	(b)MCM^{CC}	(a) MCM^{SC}	(b)MCM^{CC}	(a) MCM^{SC}	(b)MCM^{CC}
Mean	8.42	9.53	8.65	9.47	9.52	9.98	8.86	9.66
S.D.	5.69	5.88	5.29	5.45	4.5	4.53	5.2	5.32
Min.	0.26	0.47	0.32	0.43	0.75	0.84	0.26	0.43
Max.	50.74	50.74	40.94	47.32	43.38	43.9	50.74	50.74
	Variation between the means of (a) and (b): 13.18%		**Variation between the means of (a) and (b): 9.48%**		**Variation between the means of (a) and (b): 4.83%**		**Variation between the means of (a) and (b): 9.03%**	
	Continuous Explanatory Variables (Panel)				**Discrete Explanatory Variables (Panel)**			
Variable	**Mean**	**S.D.**	**Min.**	**Max.**	**Population size**	**Percentage**	**Region**	**Percentage**
HDII	0.62	0.09	0.32	0.89	Até 5	6.32%	Southeast	38.94%
HDIL	0.75	0.08	0.44	0.89	5 a10	15.40%	South	26.31%
HDIE	0.42	0.18	0.02	0.81	10 a20	25.83%	Midwest	6.84%
IND	1254.14	2870.97	0.01	74216.37	20 a50	29.25%	North	2.68%
FER	2.59	0.81	1.21	8.29	50 a100	11.64%	Northeast	25.23%
YWC	2.8	1.62	0	16.04	100 a 500	10.00%	**Total**	**100%**
PR/PU	0.67	1.31	0	63.77	500 a 1000	0.91%		
GPS	101.3	113.04	0	4702.09	>1000	0.65%		
NPS	337.39	328.91	0	8351.03	**Total**	**100%**		
NES	45.19	28.35	0	303.48				

Source: Authors' elaboration based on the STATA software.
Note: We considered 2311 observations for each period. Therefore, the panel counted on 2311 * 3 = 6933 observations.

PHE, *NHP* and *NHF* increased for the period. The mean geographical dummies (*GD*) and municipal population-sized dummies (*PSD*) indicate that 39% of the municipalities considered belong to the Southeast and approximately 29% of them have between 20 and 50 thousand inhabitants (Table 1).

Data in Table 2 indicate that standardized mortality increased in all regions between 1990, 2000 and 2010 (except Southeast, between 2000 and 2010). However, after adjustment for ill-defined causes, we note that the Southeast and South curbed their mortality rates between 2000 and 2010. Although the adjustment has increased the mortality rate in all regions, its impact was higher in the North and Northeast, with an increase of approximately 24.9% and 22% between 1990 and 2010, respectively.

The results of Table 3 reveal a significant regional difference associated with the mortality rate of breast cancer mortality in Brazil. As the Southeast region was taken as a reference (omitted), a negative coefficient associated with a region indicates that its mortality rate is lower than that of the Southeast and vice versa. Thus, Model (a), unadjusted for ill-defined causes, suggests that mortality rates are significantly higher in the South (1.31) and lower in the North (-5.02), Northeast (-3.43) and Midwest (-1.71), when compared to the Southeast, respectively.

We note that the same model, adjusted for IDC, Model (c), led coefficients associated with the South (1.11), North (-4.42) and Northeast (-2.72) regions a little bit closer to zero. Thus, after adjustment, these regions had mortality rates closer to those in the Southeast (Table 3).

In the North and Northeast, the large number of ill-defined deaths increased the relative mortality of these regions after adjustment. As both had relatively negligible rates, mortality growth (after adjustment) eventually brought them closer to the Southeast. In Table 3, the significant variation of coefficients associated to the Northeast before and after adjustment (-20.7% and -23.8%) indicates that this problem seems to affect this region intensely. Finally, the mortality rate in the Midwest was even lower than that in the Southeast after adjustment.

Table 2. Breast cancer mortality rates in Brazil and regions: 1990, 2000 and 2010.

			Crude Rates			
	Brazil	**South**	**Southeast**	**Midwest**	**North**	**Northeast**
1990	**6.82**	8.88	8.22	4.58	2.71	3.54
2000	**8.49**	11.61	9.67	6.08	2.84	4.66
2010	**11.53**	14.75	12.02	9.59	5.51	8.60
1990-2010	**8.95**	11.75	9.97	6.75	3.69	5.60
			Standardized Rates by Age Range			
	Brazil	South	Southeast	Midwest	North	Northeast
1990	**8.42**	10.55	9.84	6.98	4.26	4.85
2000	**8.65**	11.16	9.66	7.30	4.26	5.30
2010	**9.52**	11.22	9.62	8.96	6.19	8.09
1990-2010	**8.86**	10.98	9.71	7.75	4.90	6.08
			Standardized Rates by Age Range and adjusted for ill-defined causes			
	Brazil	South	Southeast	Midwest	North	Northeast
1990	**9.53**	11.34	10.67	7.72	5.63	6.81
2000	**9.47**	11.58	10.41	7.69	5.64	6.72
2010	**9.98**	11.53	10.07	9.19	7.08	8.74
1990-2010	**9.66**	11.48	10.38	8.20	6.12	7.42
			Variation between adjusted and unadjusted rates			
	Brazil	South	Southeast	Midwest	North	Northeast
1990	**13.18%**	7.49%	8.43%	10.60%	32.16%	40.41%
2000	**9.48%**	3.76%	7.76%	5.34%	32.39%	26.79%
2010	**4.83%**	2.76%	4.68%	2.57%	14.38%	8.03%
1990-2010	**9.03%**	4.55%	6.90%	5.81%	24.90%	22.04%

Source: Authors' elaboration.

The trend variable, Model (a), indicates that there was a significant increase in mortality between 1990 and 2010. According to Model (b), still unadjusted for ill-defined causes, the Northeast (1.62), Midwest (0.99), North (0.96) and South (0.33) regions were the main responsible for this growth (Table 3). In the Southeast, where the value obtained was not significant, it can be inferred that mortality remained stable in the analyzed period.

However, after IDC adjustment, Model (c), this growth trend is reduced by almost 60%. This result is directly related to declining deaths from IDC in this period. In regional terms, Model (d), it is noted that mortality is more intensely reduced in the Southeast, where the decline becomes negative and significant (-0.30) and in the South, where the trend coefficient becomes non-significant (0.10) (Table 3).

The analysis of municipal dummies without adjustment for IDC, Models (a) and (b), indicates that the lowest mortality rates are found in cities with 10-20 and 20-50 thousand inhabitants (coefficients of -3.37 and -3.34, respectively). The largest would occur in municipalities with more than 1 million inhabitants (4.05) and those with a population between 500 thousand and 1 million (1.78). It should be noted that these coefficients' reference is small municipalities, where the population does not reach 5 thousand (omitted).

After adjustment, Models (c) and (d), a lower mortality was noted in municipalities with 5 to 500 thousand inhabitants about those with less than 5 thousand ($p < 5$). As these municipalities already had lower rates than the municipalities "$p < 5$", the gap between them increased. The mortality of large municipalities, with a population of more than 500 thousand inhabitants, also grew less than the municipalities "$p < 5$" after adjustment. However, as the mortality of these large cities was higher than the others, their rates drew closer to those of "$p < 5$" municipalities. In the case of cities with a population between 500 thousand and 1 million inhabitants, the difference became insignificant with regard to the "$p < 5$" municipalities. Therefore, the problem caused

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Table 3. Effect of adjustment for deaths due to ill-defined causes on the discrete variables associated with breast cancer mortality. Brazil, 1990-2010.

	Unadjusted		Adjusted		Variation	
	(a)	(b)	(c)	(d)	[(c-a)/a]	[(d-b)/b]
South	1.314***	0.425	1.117***	0.322	-15.0%	(-24.2%)
Midwest	-1.712***	-3.913***	-1.917***	-3.984***	12.0%	1.8%
North	-5.023***	-7.172***	-4.420***	-6.467***	-12.0%	-9.8%
Northeast	-3.429***	-6.895***	-2.718***	-5.252***	-20.7%	-23.8%
Southeast	Omitted	Omitted	Omitted	Omitted		
Overall trend	0.548***		0.221**		-59.7%	
Trend South		0.335*		0.096		(-71.3%)
Trend Midwest		0.990***		0.732**		-26.1%
Trend North		0.964*		0.722		(-25.1%)
Trend Northeast		1.623***		0.966***		-40.5%
Trend Southeast		-0.110		-0.302**		(174.5%)
p<5	Omitted	Omitted	Omitted	Omitted		
p. 5-10	-2.499***	-2.499***	-2.802***	-2.802***	12.1%	12.1%
p. 10-20	-3.374***	-3.374***	-3.622***	-3.622***	7.4%	7.4%
p. 20-50	-3.345***	-3.345***	-3.769***	-3.769***	12.7%	12.7%
p. 50-100	-2.573***	-2.573***	-3.059***	-3.059***	18.9%	18.9%
p. 100-500	-0.826**	-0.826**	-1.209***	-1.209***	46.4%	46.4%
p. 500-1000	1.783**	1.783**	1.215	1.215	(-31.9%)	(-31.9%)
p>1000	4.050***	4.050***	3.222***	3.222***	-20.4%	-20.4%
Constant	11.114***	12.431***	12.776***	13.821***	15.0%	11.2%
Obs.	6933	6933	6933	6933	-	-
R^2	0.21	0.22	0.16	0.16	-	-
AIC	40951.98	40853.51	41708.71	41663.36	-	-
BIC	41040.95	40969.86	41797.69	41779.71	-	-
Post	13	17	13	17	-	-

Source: Own elaboration based on the STATA software.

Notes: 1) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; 2) Estimates via Pooled Ordinary Least Squares (POLS); 3) The percentages between parentheses considered non-significant coefficients.

by ill-defined deaths tends to increase more pronouncedly mortality in cities with less than 5 thousand inhabitants.

The fixed-effect estimates (FE) of Table 4 were shown to be preferable, according to the Hausman's test (1978), for both the model without adjustment for IDC, Model (c) and the adjusted one, Model (f). Results of Model (c) indicate that there is a positive and significant association of income (*HDII*) and longevity (*HDIL*) with mortality due to breast cancer. Meanwhile, education (*HDIE*), fertility rate (*FER*), and public health expenditure (*PHE*) would have a negative and significant relationship. In Model (f), with adjustment, we noted a loss of significance of part of the variables that had been significant in the model without adjustment. Among these, *FER*, *HDIE* and *HDII* were the most affected by the adjustment. Reduction of the coefficients of these variables was 95.3%, 74.8% and 61.5%, respectively. Only *HDIL* and *PHE* remained significant. However, the adjustment revealed that estimates, unadjusted for IDC, may be overestimating the effect of longevity (by almost 33%) and of Public Health Expenditure (by a little more than 6%) on the rate of breast cancer mortality in Brazil.

Discussion and conclusion

Mortality indicators are an essential input for the diagnosis of health. In Brazil, such data are provided by the Mortality Information System (SIM), implemented by the Ministry of Health between 1975 and 1976. Although this system increases its coverage and improves the quality of

Table 4. Effect of adjustment for deaths due to ill-defined causes on the continuous variables associated with breast cancer mortality. Brazil, 1990-2010.

	Unadjusted			Adjusted			Variation		
	(a) POLS	(b) RE	(c) FE	(d) POLS	(e) RE	(f) FE	[(d-a)/a] POLS	[(e-b)/b] RE	[(f-c)/c] FE
HDII	21.640***	20.894***	6.139*	21.039***	20.356***	2.365	-2.78%	-2.57%	(-61.48%)
HDIL	4.362*	5.346**	9.301***	2.540	3.218	6.238*	(-41.77%)	(-39.81%)	-32.93%
HDIE	-5.624***	-5.723***	-2.254*	-5.352***	-5.332***	-0.569	-4.84%	-6.83%	(-74.76%)
IND	0.052*	0.047*	-0.003	0.028	0.025	-0.015	(-46.15%)	(-46.81%)	(400.00%)
FER	-0.685***	-0.636***	-0.387*	-0.468***	-0.382**	-0.018	-31.68%	-39.94%	(-95.35%)
YWC	-0.179***	-0.157***	-0.050	-0.196***	-0.172***	-0.032	9.50%	9.55%	(-36.00%)
PR/PU	-0.021	-0.018	0.001	-0.010	-0.004	0.022	(-52.38%)	(-77.78%)	(2100.00%)
GPS	-0.022	-0.097	-0.186*	-0.086	-0.140*	-0.174*	(290.91%)	(44.33%)	-6.45%
NPS	0.028	0.014	-0.036	0.049*	0.033	-0.029	(75.00%)	(135.71%)	(-19.44%)
NES	0.184	0.065	-0.003	0.115	0.014	0.051	(-37.50%)	(-78.46%)	(-1800.00%)
CTE.	-3.480**	-3.717**	0.473	-1.524	-1.755	4.148	(-56.21%)	(-52.78%)	(776.96%)
R^2	0.16	0.16	0.14	0.11	0.11	0.08	-	-	-
R^2_b		0.28	0.25		0.23	0.17	-	-	-
R^2_w		0.03	0.03		0.00	0.01	-	-	-
AIC	41346.72	.	36720.94	42032.87	.	37509.62	-	-	-
BIC	41422.00	.	36796.23	42108.16	.	37584.90	-	-	-

Notes: 1) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; 2) The percentages between parentheses considered non-significant coefficients. Hausman's test (1978): (c) versus (b): χ^2=524.91; Prob.> χ^2=0.000. (f) versus (e): χ^2=523.41; Prob.> χ^2=0.000 .

its data, deaths from ill-defined causes (IDC) are still reported, which may compromise the analysis of mortality, especially that for specific causes[23]. Deaths from ICD accounted for 18.2% of total deaths in the country in 1991. This percentage fell to 15.1% in 1996, 14.9% in 1996, 13.3% in 2003 and 8.6% in 2010[23,48,49]. Despite this decline, a still considerable portion of Brazilian deaths are still ill-defined, mainly in the North and Northeast[19,27-29].

With respect to breast cancer mortality, studies that use adjustment methods for IDC[10,19] have been developed only recently. Thus, we made an effort in order to identify the main distortions caused by ill-defined deaths on the analysis of breast cancer mortality in Brazil. As such, it is possible to evaluate how the results of works that disregard this adjustment could be compromised.

Initially, it was noted that IDC adjustment increased the breast cancer mortality rate of Brazilian municipalities by slightly more than 9% between 1990 and 2010. A small value when compared to the 103.3% increase verified by Gamarra et al.[28], for the case of cervical cancer in Brazil between 1995 and 2006.

Also, the impact of ill-defined deaths decreased over the period considered (the increase in the adjusted mortality rate fell from 13.2% in 1990 to 4.8% in 2010). This trend of reduced readjustment derived from IDC correction was also verified by Malta et al.[29] for lung cancer in men and women (an increase of 21.1% and 36.8% in 1996 and 10.6% in 10.1% in 2010, respectively). These results are associated with improved quality of information on the underlying cause of death in the country. The proportion of Brazilian deaths from IDC decreased from 18.2% in 1990 to 7.0% in 2010[42].

The unadjusted results for IDC indicated that breast cancer mortality is higher in the South, Southeast, Midwest, Northeast and North regions, respectively. However, after adjustment, we verified that the mortality rate of the South region decreased compared to that of the Southeast, while the North and Northeast rates increased. Other studies focusing on mortality associated with chronic noncommunicable

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diseases[27], to cervical cancer[28] and lung cancer[29] also indicated that the impact of IDC adjustment would be higher in these two regions.

Meanwhile, mortality in the Midwest was even lower than that in the Southeast after correction. These results indicate that, in the analyzed period, the quality of death records was proportionally better in the South and Midwest regions and worse in the North and Northeast, when compared to the Southeast.

The analysis unadjusted for IDC revealed a significant elevation in the mortality rate from breast cancer between 1990 and 2010. The Northeast, Midwest, North and South regions were the primary responsible for this hike. Mortality remained stable in the Southeast.

However, after adjustment, this growing trend was reduced by almost 60%, which is directly related to declining deaths from IDC for the period. The most considerable reductions occurred in the Southeast (which, in this case, started to show a negative and significant trend) and South (where the growth trend, previously verified, was replaced by a stable mortality rate).

The unadjusted results also indicated that the lowest mortality rates are found in cities with 10 to 50 thousand inhabitants. On the other hand, the largest would occur in municipalities with more than 500 thousand inhabitants and where the population is less than 5 thousand inhabitants, respectively.

After adjustment, we verified that the mortality growth of municipalities of 5 to 500 thousand inhabitants was lower than those with less than 5 thousand inhabitants, increasing the gap between the mortality rates of these two groups. The mortality of large municipalities, with a population of more than 500 thousand inhabitants, also grew less than that of municipalities with less than 5 thousand inhabitants. However, as the mortality of these large cities was relatively higher, their rates drew closer. Therefore, IDC adjustment tends to increase, in a more pronounced way, the mortality of small towns with less than 5 thousand inhabitants.

The analysis unadjusted for IDC indicated a positive and significant association of income and longevity with mortality from breast cancer. On the other hand, education, fertility rate and public health expenditures showed a negative and significant relationship. After adjustment, only longevity and public health expenditure remained significant. However, outcomes unadjusted for IDC were overestimating the effect of longevity (by almost 33%) and of public health expenditure (by a little more than 6%) on the breast cancer mortality rate in Brazil.

It should be noted that the use of aggregated secondary data and the impossibility of including some factors associated with breast cancer mortality (possible confounding sources) are a limitation of this work. Furthermore, the analysis of mortality over 20 years involves other aspects that are difficult to incorporate into the models (*e.g.*, advances/changes in death registers, diagnoses and treatments for breast cancer). Finally, the ill-defined adjustment technique used in this research does not allow us to identify the actual cause of death and may have inflated mortality rates, especially where there are more undefined deaths.

Despite this, the results highlight the possible biases that could be caused by ill-defined deaths in the analyses of mortality associated with breast cancer. Therefore, neglecting such an effect could undermine a reliable analysis of the health situation, thereby compromising the adoption of adequate public policies and health planning in the country.

Collaborations

MAS Couto: author of the work, coming from Master's research. MT Bustamante-Teixeira and MR Guerra: contributed in areas such as literature review, selection and data collection and analysis of results. Firm VAC: contributed to the elaboration and estimation of regression models .: contributed in areas such as literature review, selection and data collection and analysis of results.

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