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Impact of redistributing deaths by ill-defined causes in oral and oropharyngeal cancer mortality in Brazil

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Abstract: Less-than-optimal reliability of mortality information systems regarding the underlying cause of death can mask the reality of oral (OC) and oropharyngeal cancer (OPC) mortality. This study aimed to assess the impact on the magnitude and temporal trends of OC and OPC mortality in Brazil of two statistical approaches to redistribute deaths with ill-defined underlying causes. We analyzed deaths with ill-defined causes in Brazil by macro-region, between 1996-2018. The Mortality Information System provided official information on deaths. Two correction methods were applied: the EF method, which proportionally reallocates deaths classified as R00-R99 in the ICD-10 to the remaining specific causes of death according to the proportion of deaths with certified causes; and the GBD method, which considers the concept of garbage codes, redistributing deaths from several ICD-10 chapters according to previously established coefficients. For the trend analysis of mortality (certified and redistributed), the Prais-Winsten method was carried out. The OC and OPC death rates had an evident increase after the redistribution by the two techniques in all regions of the country; the increase was higher using the GBD method. In the Northeast and North regions, this method more than doubled the certified death rates. The redistribution methods also changed time series trends. In epidemiological studies of mortality from OC and OPC, it is necessary to redistribute deaths from ill-defined causes when analyzing data from less-than-optimal information systems. The choice of the correction method is critical; epidemiological studies must manage it as a methodological decision that has significant impacts on results.

Keywords: Mouth Neoplasms; Oropharyngeal Neoplasms; Mortality; Health Information Systems.

Introduction

Oral (OC) and oropharyngeal (OPC) cancers are a relevant cause of mortality worldwide. In 2017, they caused about 4% of all cancer deaths in the world.[1] This percentage accounted for more than 220,000 deaths in 2018, according to the International Agency for Research on

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Cancer (IARC). Mortality from these malignancies varies widely by region, and OC is the second most common cancer leading to death in regions like South Central Asia.[2] The mortality rate form OC and OPC estimated by IARC for Brazil in 2020 was 4.9 deaths per 100,000 inhabitants in men in 2020, which was much higher than in Latin America and the Caribbean: 2.6/100,000.[3]

Tracking oral cancer is one of the priorities of the World Health Organization's non-communicable diseases and universal health coverage agenda.[4] Monitoring the magnitude and time trends of OC and OPC mortality is a tool for understanding their dynamics across time and defining public health policy and programming. This measure becomes more critical in the absence of reliable records of cancer incidence, which is the reality in several countries, such as Brazil.[5] Besides, monitoring mortality trends is critical to understand recent changes in the etiology of OC and OPC (*i.e.*, the increasing involvement of HPV virus as a risk factor for OPC).

In Brazil, the Mortality Information System (SIM) gathers the data from death records across the country since 1975/76.[6] In the last decades, researchers have analyzed the quality of the SIM, observing the two leading indicators of reliability of an information system: the coverage and completeness of the cause of death registration. The results show remarkable improvements in the quality of data in the last 20 years.[7,8] However, SIM reliability varies between regions of the country, and some consistency issues persist,[9,10] especially in the most impoverished areas.[11]

The development of strategies to deal with the reliability of mortality information systems is an international concern, and this is no different in Brazil.[12,13] In 2016, Brazil joined an international initiative to qualify information on causes of death, the Data for Health Initiative, along with 19 other countries. This collaboration triggered a series of SIM evaluation studies and interventions to qualify the records, mainly aimed at correcting "garbage codes" – according to Naghavi et al.,[12] these are "all deaths assigned to codes that should be redistributed to enhance the validity of public health analysis". However, these initiatives were primarily aimed at directly reclassifying ill-defined deaths, and although it produces highly reliable data, it is not an easily implemented alternative.[14]

Various statistical approaches to dealing with this challenge by redistributing ill-defined deaths are currently proposed in the literature, and they differ substantially from one another.[15-19] Some methodologies assume that only deaths with ill-defined codes (Chapter XVIII of the ICD-10) are redistributed, while others extend redistribution to codes from other chapters – *i.e.*, adopting the concept of "garbage codes". The strategies for redistribution also vary in methodological complexity.[20] These redistribution methods are usually used for epidemiological studies and are not directly applied to data in the information systems. However, influential epidemiological studies that feed publicly available databases, like the Global Burden of Disease Study, provide global estimates already corrected for garbage codes.[18] In Brazil, the SIM provides data with the registered cause of death, and the Brazilian Ministry of Health makes data available (by ICD-10 chapter) through an official website after applying a method for sub-record correction; however, data corrected for garbage codes are not available in official databases or websites.

Despite the interest in redistribution strategies, there is a lack of knowledge about how each correction strategy impacts results. In studies on OC and OPC mortality, it is not rare to find methodologies that entirely neglect the correction of ill-defined deaths, and, in most of them, correction procedures are applied without justifying their choice or discussing their impact. The objective of this study was to assess the impact on the magnitude and temporal trends of OC and OPC mortality of two statistical indirect approaches of redistribution of deaths with ill-defined underlying causes. The two techniques are presented in detail in the literature, which allows their replicability, and have been applied in cancer mortality studies worldwide and in Brazil.

Methodology

This study analyzed deaths with ill-defined causes that occurred in Brazil between 1996 and

2018. The SIM of Brazil, maintained by the Ministry of Health, provided official information on deaths, broken down by place of residence. The macro-region division is an official territorial organization of Brazil that distributes the twenty-six states and the Brazilian Federal District in five major regions: North, Northeast, Southeast, South, and Midwest.

The lower limit of the analyzed period is the year in which the SIM started using the International Classification of Diseases - tenth revision (ICD-10) for coding the underlying causes of death. We collected all deaths whose primary cause was oral cancer and oropharyngeal cancer, based on the classification proposed by Chaturvedi et al.[21] – the codes are detailed in Table 1. Deaths that did not have information on age, sex, or town of residence were allocated based on the known distribution of these characteristics by region.

We obtained data on resident population from the Demographic Census carried out by the Brazilian Institute of Geography and Statistics in 1991, 2000, and 2010. Based on these data, we calculated within-census estimates using linear trends. Mortality rates due to oral or oropharyngeal cancer were calculated per 100,000 inhabitants for each macro-region. These rates were adjusted by sex and age (in 5-year intervals) using the direct method and the standard distribution of population defined by the World Health Organization.[22]

Two different methods were applied to distribute deaths with ill-defined causes. The first one was based on the method proposed by França et al.,[15] the "EF method". This technique proportionally reallocates deaths classified as R00-R99 of the ICD-10 – chapter XVIII – to the remaining specific causes of death according to the proportion of deaths with certified causes. However, it considers that deaths from cancer have a lower chance of being registered with "R" codes and proposes the redistribution of only half of the proportion that would be assigned to this disease. Following the description of Bigoni, Cunha, Antunes[20] (2021), this technique can be summarized by the following formula:

$$0.5 * NDr * \left(\frac{NDc}{AD - NDr - NE}\right)$$

Table 1. International Classification of Diseases, tenth revision (ICD-10) codes included in the categories of "oral cancer" and "oropharyngeal cancer".

Oral cancer (Malignant neoplasm of…)	ICD-10
dorsal surface of tongue	C02.0
border of tongue	C02.1
ventral surface of tongue	C02.2
tongue, part unspecified	C02.3
overlapping lesion of tongue	C02.8
tongue, unspecified	C02.9
upper gum	C03.0
lower gum	C03.1
gum, unspecified	C03.9
anterior floor of mouth	C04.0
lateral floor of mouth	C04.1
overlapping lesion of floor of mouth	C04.8
floor of mouth, unspecified	C04.9
hard palate	C05.0
soft palate	C05.1
uvula	C05.2
overlapping lesion of palate	C05.8
palate, unspecified	C05.9
cheek mucosa	C06.0
vestibule of mouth	C06.1
retromolar area	C06.2
overlapping lesion of other and unspecified parts of mouth	C06.8
mouth, unspecified	C06.9
Oropharyngeal Cancer (Malignant neoplasm of…)	**ICD-10**
base of tongue	C01
lingual tonsil	C02.4
tonsillar fossa	C09.0
tonsillar pillar (anterior) (posterior)	C09.1
overlapping lesion of tonsil	C09.8
tonsil, unspecified	C09.9
vallecula	C10.0
anterior surface of epiglottis	C10.1
lateral wall of oropharynx	C10.2
posterior wall of oropharynx	C10.3
branchial cleft	C10.4
overlapping lesion of oropharynx	C10.8
oropharynx, unspecified	C10.9
Waldeyer ring	C14.2

Where *NDr* is the number of deaths from the ICD-10 chapter XVIII; *NDc* is the certified number of deaths by oral or oropharyngeal cancer; *AD* is the total number of deaths; *NE* is the number of deaths by external causes – which would have been correctly recorded because autopsy is mandatory in Brazil for these deaths.

The second method for redistributing ill-defined deaths was based on the methodology of the 2010 Global Burden of Disease Study (GBD). In this technique (the "GBD method"), the concept of poorly registered deaths is expanded, and the terminology "garbage codes" is adopted.[16] This concept covers codes from several chapters of the ICD-10, and the GBD 2010 indicates which groups of garbage codes should be redistributed (and in what proportion) for each underlying cause of death studied. Considering only the application for cancer, the method can be summarized by the following formula, as proposed by Bigoni, Cunha and Antunes:[20]

$$NDc + \sum ND_{gi} * C_i$$

Where *NDc* is the number of deaths by oral cancer or oropharyngeal cancer (certified); *i* is the garbage code group; *NDgi* is the number of deaths by a garbage code group; and *C* is the coefficient, which indicates the proportion of the group that must be redistributed to cancer. The groups of garbage codes and the coefficients proposed to correct deaths from oral cancer and cancer of other parts of the pharynx and oropharynx are presented in the GBD 2010 publication.[16] For the correction of oral and oropharyngeal cancer cases only, we adapted this method by deducting the proportion of salivary gland and hypopharyngeal neoplasms from the coefficient.

For the trend analysis of mortality, a generalized linear regression using the Prais-Winsten method was carried out – the death rate logarithm was the dependent variable. This analysis was made for rates based on certified deaths and for rates corrected by the two redistribution methods, by macro-region. The Prais-Winsten method performs first-order autocorrelation correction: a common problem in the analysis of temporal series. It also quantifies the yearly rate change, allowing the calculation of the Annual Percent Change (APC) and its 95% confidence interval ($CI_{95\%}$):[23]

$$APC = (-1 + 10^{b1}) * 100\%$$
$$CI_{95\%}{}^{lower} = (-1 + 10^{b1lower}) * 100\%$$
$$CI_{95\%}{}^{upper} = (-1 + 10^{b1upper}) * 100\%$$

Where *b1* represents the regression coefficient and *b1lower*/*b1upper* are its $CI_{95\%}$ limits. Mortality was classified as increasing when APC and its $CI_{95\%}$ were positive, decreasing, when they were negative, and stationary, when they included the zero.

The initial and final magnitudes of the rates were determined: the former corresponded to the average rate for 1996 to 1998 and the latter to the average rate for 2016 to 2018. Finally, we obtained the Rate Ratio (RR) between the certified and corrected rates (corrected rates divided by rates of certified data) and calculated the APC of RR.

Results

Death rates of oral and oropharyngeal cancer in Brazil from 1996 to 2018 had an evident impact after the redistribution of ill-defined deaths by the two methods; the increase in rates was higher using the GBD technique. The discrepancy between the certified and corrected rates was higher during the first half of the series and in the North and Northeast regions (Figures 1 and 2).

Regarding oral cancer, the Southeast region had the highest initial (certified: 1.62/100,000 inhabitants; EF: 1.71; GBD: 2.34) and final (certified: 1.44; EF: 1.47; GBD: 1.90) death rates. Mortality underwent a decreasing trend in the Southeast in all scenarios and this was the only region where the trend in the three scenarios was the same. In general, trends assessed for corrected estimates had lower figures of APC. When the APC was positive, correction methods generated a less pronounced increase in rates than for non-corrected rates. When the APC was negative, correction methods generated a more pronounced decrease (Table 2).

The highest final (certified: 1.56; EF: 1.63; GBD: 2.20) and initial (certified: 1.47; EF: 1.50; GBD: 1.88) death rates of oropharyngeal cancer were identified

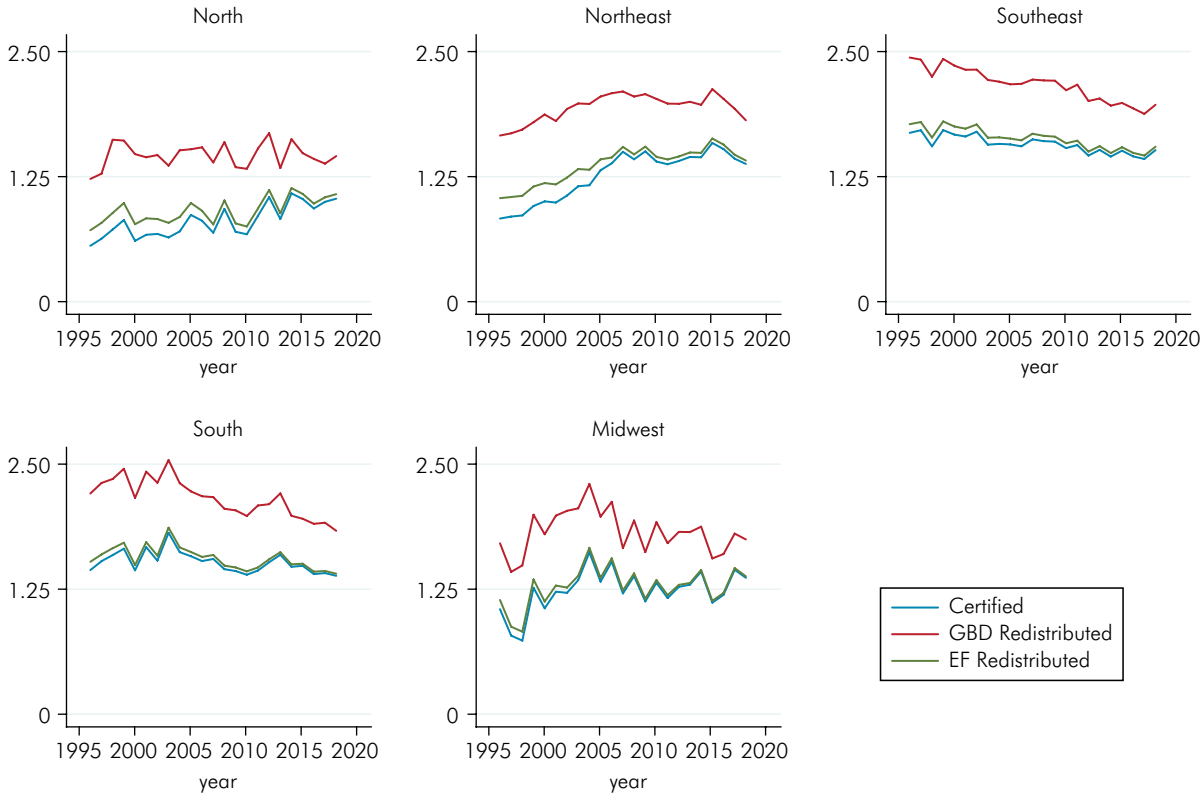

Figure 1. Oral cancer mortality, Brazil, 1996-2018. Certified and redistributed death rates by macro-region, both sexes, per 100,000 inhabitants.

in the Southeast region. In the South and Midwest regions, the trend identified by the GBD method was different from the others. Certified deaths in the Northeast had the highest APC (4.34%; increasing trend); mortality redistributed by the GBD method in the Southeast had the lowest APC (-0.84; decreasing trend). With few exceptions, the initial and final death rates of oral cancer were higher than those of oropharyngeal cancer (Table 2).

The correction by the GBD method generated the highest death rates. In the Northeast and North, for both types of cancer, this method more than doubled certified death rates (initial magnitude). The correction by the EF method had a lower impact on the magnitude of rates, only discretely increasing them. For the two types of cancer, both at the beginning and end of the study period, redistributing ill-defined deaths mainly impacted the North and Northeast regions by increasing the resulting rates. The rate ratio – RR comparing certified and redistributed death rates had a statistically significant decreasing trend for both methods and both types of cancer, in all regions (Table 3).

Discussion

This study assessed the application of two indirect methods of correcting ill-defined deaths from OC and OPC in Brazil from 1996 to 2018. In comparison with certified deaths, both methods – EF and GBD – resulted in higher rates and, in some regions, they even changed the rate's temporal trend. The impact of the correction method was different, indicating that this is not a mere methodological formality. In countries like Brazil, where there's no nationwide information system on cancer incidence, it is even more important to recognize the difference between confirmed and corrected rates; it is mainly the mortality data that allow us to understand the dynamics of this disease. As far as we know, this is the first study that analyzes techniques for correcting ill-defined deaths for OC and OPC specifically.

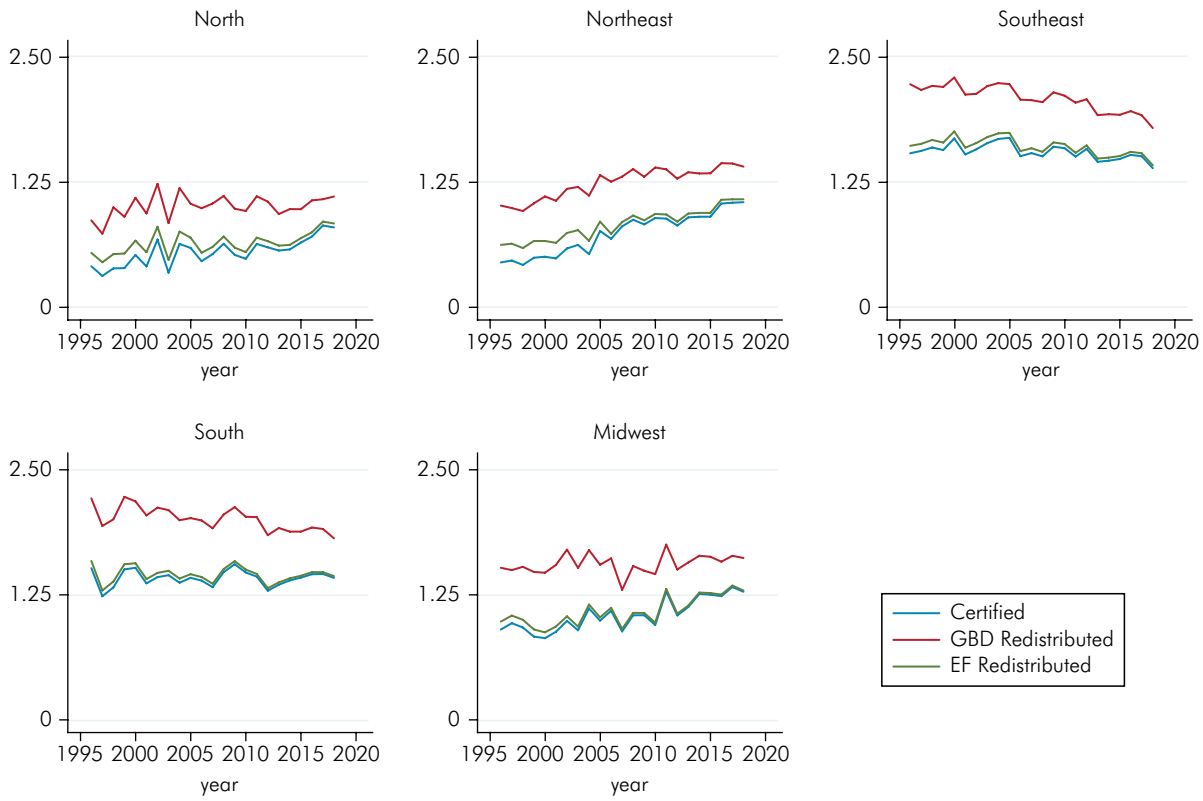

Figure 2. Oropharyngeal cancer mortality, Brazil, 1996-2018. Certified and redistributed death rates by macro-region, both sexes, per 100,000 inhabitants.

Table 2. Certified versus redistributed mortality of oral and oropharyngeal cancer by the EF and GBD methods by macroregion, for 100,000 inhabitants: initial and final magnitude, annual percent change (APC), and trends. Brazil, 1996-2018.

Variable	Oral cancer					Oropharyngeal cancer				
	N	NE	SE	S	MW	N	NE	SE	S	MW
Initial magnitude										
Certified	0.63	0.82	1.62	1.44	0.84	0.37	0.44	1.56	1.36	0.94
EF Redistributed	0.79	1.02	1.71	1.51	0.93	0.51	0.61	1.63	1.43	1.01
GBD Redistributed	1.37	1.66	2.34	2.21	1.53	0.86	0.99	2.20	2.05	1.52
Final magnitude										
Certified	0.96	1.41	1.44	1.34	1.29	0.77	1.04	1.47	1.45	1.29
EF Redistributed	1.00	1.45	1.47	1.36	1.31	0.81	1.07	1.50	1.47	1.30
GBD Redistributed	1.39	1.89	1.90	1.82	1.68	1.08	1.42	1.88	1.88	1.62
APC & Trend										
Certified	2.37	2.66	-0.69	-0.45	1.38	3.02	4.34	-0.42	0.05	1.86
	↑	↑	↓	↔	↑	↑	↑	↓	↔	↑
EF Redistributed	1.33	1.73	-0.84	-0.60	1.01	1.59	2.72	-0.56	-0.10	1.50
	↑	↑	↓	↓	↔	↑	↑	↓	↔	↑
GBD Redistributed	0.12	0.55	-1.07	-1.04	-0.09	0.64	1.71	-0.84	-0.61	0.29
	↔	↔	↓	↓	↔	↑	↑	↓	↓	↔

↑ Increasing trend; ↓ Decreasing trend; ↔ Stationary trend; N: North; NE: Northeast; SE: Southeast; S: South; MW: Midwest; Death rates were previously standardized by age and sex.

Table 3. Certified versus redistributed mortality for oral and oropharyngeal cancer by the EF and GBD methods by macroregion, for 100,000 inhabitants: Rate Ratio (RR) of the final and initial magnitudes (redistributed/certified), annual percent change (APC), and trend of RR. Brazil, 1996-2018.

Variable	Oral cancer					Oropharyngeal cancer				
	N	NE	SE	S	MW	N	NE	SE	S	MW
RR of initial magnitude										
Certified	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
EF Redistributed	1.25	1.24	1.05	1.05	1.10	1.37	1.38	1.05	1.05	1.08
GBD Redistributed	2.17	2.02	1.44	1.54	1.81	2.35	2.22	1.41	1.51	1.62
RR of final magnitude										
Certified	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
EF Redistributed	1.05	1.03	1.02	1.02	1.01	1.05	1.03	1.02	1.01	1.01
GBD Redistributed	1.45	1.34	1.32	1.36	1.30	1.40	1.37	1.28	1.30	1.26
APC & Trend of RR										
EF Redistributed	-0.99	-0.93	-0.15	-0.16	-0.36	-1.40	-1.44	-0.14	-0.15	-0.34
	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
GBD Redistributed	-2.19	-2.08	-0.39	-0.59	-1.46	-2.31	-2.51	-0.40	-0.66	-1.50
	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓

↑ Increasing trend; ↓ Decreasing trend; ↔ Stationary trend; N: North; NE: Northeast; SE: Southeast; S: South; MW: Midwest; death rates were previously standardized by age and sex.

The two methods we applied have essential methodological differences. The EF method allows the redistribution of ill-defined deaths, which are those registered with codes from chapter XVIII of ICD-10 (the "R" codes), while the GBD technique redistributes a range of other causes defined as "garbage codes", in addition to the R codes. This category covers deaths registered with codes that should not be listed as the primary cause of death because a) they are immediate or intermediate causes of the disease chain that led to death or b) they are causes that do not lead to death. This is the probable reason why the EF technique's results were more conservative than those of the GBD: the concept of ill-defined deaths is less comprehensive. Considering these differences, it is essential to highlight that in Brazil, 5.4% of deaths registered in the SIM in 2015 had an R code as the underlying cause, while 26.34% were registered with non-R garbage codes.[11]

Considering the EF technique, the percentage that we redistributed from ill-defined deaths to deaths by OC and OPC corresponds to an estimate for all cancers because unlike the GBD method, this method does not propose coefficients by cancer type. Almost half of the OC and OPC cases are diagnosed in advanced stages – stages III or IV[24]. Large tumors may spread from their primary site, thus preventing their identification. Considering this particularity, perhaps a different proportion of poorly registered deaths should be redistributed to OC and OPC; this proportion would be larger than that defined for all types of cancer by the EF technique. This assumption is anchored in the evidence that "other and unspecified parts of the mouth" – which is the most nonspecific code related to oral topographies – is the category with the highest proportion of mortality among oral cancers in Brazil.[25]

The impact of redistribution methods was also observed for the APC, which is a significant finding because monitoring incidence and mortality trends is a strategic tool for OC and OPC's surveillance related to risk factors.[26] With the absence of population-based cancer records that inform the tumor's etiology and the increased involvement of the HPV virus as a risk factor for OPC, comparing the populational behavior of OC (which is site not related to HPV) with that of OPC (HPV-related) provides clues about their etiology.[26-28] This comparison serves as an alternative

assessment of the virus's potential carcinogenic effect.[21] Our findings indicate that analyses based only on death certificate data can mask trends and lead to mistaken etiological hypotheses.

Deaths with ill-defined primary cause are more frequent among older adults than in the other age groups.[7,11] Considering that the correction methods used general coefficients to redistribute ill-defined deaths (*i.e.*, the same for different age groups), they may be underestimating the number of deaths that should be redistributed to older adults. Since OC and OPC deaths also mostly affect older adults, this inaccuracy may be relevant in the context of our results, meaning that mortality might be even higher than what has been obtained with the correction of estimates by the application of the EF and GBD methods.

In the initial part of the study period, the GBD method more than doubled mortality from oral cancer in the North and Northeast, while the correction's impact was less pronounced in the other regions, which indicated a higher proportion of garbage codes in those two regions. A recent study that corrected deaths from noncommunicable diseases in Brazilian municipalities also identified clusters with higher proportions of garbage codes in the North and Northeast[19]. However, in the final period of the study, the difference between corrected and registered deaths was more homogeneous between regions, indicating that these two regions partially compensated for their disadvantage in the quality of death registration data. For oral cancer, correction methods changed the time trend of rates in the North, Northeast, South, and Midwest regions. This means that the qualification of death registries in this historical series has been masking the real mortality trend from oral cancer in these four regions. The results from the Southeast, which were the exception in this analysis, may be reflecting two phenomena: a) lower impact of redistribution methods on temporal trends due to the lower proportion of garbage codes since the start of the series – the results expressed in Table 2 indicated that the Southeast region presented the smallest difference between the certified and corrected rates at the beginning of the series; and b) a stronger real temporal trend (decrease) than in the other regions, which not even the qualification of the registry was able to mask.

The results of the rate ratio that compares certified and redistributed death rates indicate a relevant reduction in the number of ill-defined deaths in the country between 1996 and 2018, regardless of the correction technique. This result is in line with other evidence of qualification of death records in Brazil in recent decades,[11] and it does not appear to be due to chance. Several initiatives aimed at qualifying the death registry worldwide and in Brazil are presented in the literature, ranging from advanced methods for assessing the problem to direct training of registrars, supported by international collaboration.[14,29,30] The reduction in the number of poorly registered deaths was more significant in the country's poorest regions, in which death records are historically more precarious (North and Northeast), suggesting that these initiatives are reaching the weakest points of the system.

We adopted the Chaturvedi classification to define which ICD-10 codes should comprise the OC and OPC[21] categories, which is a limitation of this study because it is not the only classification internationally accepted[28]. Also, in the GBD method, we employed the correction technique used in the GBD 2010 Study. Since then, the Institute of Health Metrics and Evaluation has developed more sophisticated versions of the statistical corrections for garbage codes.[18] Our rationale for choosing this less recent technique is its applicability: the new versions require advanced technical expertise and make reproducibility difficult for researchers external to the project.

This study does not allow us to define which of the two techniques is more accurate. For this, they would have to be compared to a gold standard method, in which each ill-defined death is investigated through analysis of health service records or verbal autopsy. Brazilian researchers developed a study with a methodology similar to that used for infant mortality, which produced a correction method that the Brazilian Ministry of Health adopted as a correction strategy.[13] The results of applying this method are available in the country's official databases; however, they do not provide corrections by cancer subtype, but only by

ICD-10 chapter, making the comparison with the data of the present study not feasible. We emphasize that indirect correction methods are also imperfect and, although more feasible than direct reclassifications, are based on generalized concepts that can result in inaccuracies. The available redistribution methods cannot replace registry qualification efforts.

Conclusions

The present study suggests that mortality by OC and OPC is higher than informed by Brazil's Mortality Information System. Even considering the rates of the most recent period (2016 to 2018), a significant portion of deaths due to OC and OPC is hidden by low quality death certification. This problem is probably not restricted to Brazil; it is the likely scenario in all countries with a non-negligible proportion of poorly registered deaths. This study concludes that, in epidemiological studies of OC and OPC mortality, it is necessary to redistribute deaths from ill-defined causes when analyzing data from less-than-optimal information systems. The choice of correction method is critical and must be managed in epidemiological studies as a methodological decision that may have a significant impact on results. Researchers should justify, discuss, and, if possible, even compare correction methods before presenting mortality data for OC and OPC to avoid misrepresenting the burden of this disease and the challenges revealed by data analysis.

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