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Thyroid cancer mortality in Brazil and its geographic regions: mortality trends and projections until 2030

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ABSTRACT

The objective of this study was to analyze temporal trends for thyroid cancer mortality in Brazil and its geographic regions, in the period 2001-2015, and calculate mortality projections until 2030. Methods: An ecological study is presented herein on thyroid cancer-related deaths in Brazil, based on the registries of the Mortality Information System. Mortality trends were analyzed by Joinpoint regression, and the Nordpred software (within the R program) was utilized for the calculation of projections. Results: An adjusted mortality rate (ASW) of 0.48 deaths/100,000 inhabitants was obtained for women and 0.27 deaths/100,000 inhabitants for men, with a significant decreasing trend for the female sex (APC= -1.6; CI95%: -2.5; -0.6), while for the male sex the mortality rates decreased non-significantly (APC= -0.5; CI95%: -1.5; 0.5). Mortality rates for the female sex present a decreasing projection until 2030. For the male sex, the same characteristic is observed, however the North and Northeast regions present increasing projections, and these numbers are mainly explained by the variation in the Brazilian demographic structure. Conclusions: Thyroid cancer mortality presented decreases, more pronounced for the female sex.

KEYWORDS: Thyroid neoplasm; Trends; Projection of rates; Mortality; Epidemiology.

INTRODUCTION

Thyroid cancer is the most common endocrine neoplasm in the world[1] and classified as the 9th most incident[2]. In 2018, it was estimated that 567 thousand people, around the world, had thyroid cancer, while 41 thousand died because of the disease. The global incidence rate in women is 10.2 per 100,000 inhabitants, three times higher than in men, and represents 5.1% of the total estimated burden for female cancer. Thyroid cancer incidence rates are higher in men and women of the Republic of Korea, as well as in North America (mainly in Canada), Australia/New Zealand and Oriental Asia[2].

High-income countries present double the incidence of low/intermediate income countries: for women (11.10 per 100,000 and 4.70 per 100,000, respectively) and men (3.60 per 100,000 and 1.40 per 100,000, respectively). Regarding mortality, the opposite occurs: the majority of countries with high mortality rates are concentrated in Central America and Asia (0.6 per 100,000 women and 0.4 per 100,000 men) while low rates are found in Occidental Europe and North America (0.2 per 100,000 inhabitants, for both sexes)[3].

In Brazil, thyroid cancer corresponds to 4% of diagnosed cancers in females, representing the fifth most incident cancer in women. In the biennium 2018-2019, there is an estimated risk of 1.49 new cases per 100,000 men and 7.57 cases per 100,000 women[4]. Thyroid cancer was responsible for 784 deaths in 2015, with adjusted mortality rate 0.39 per 100,000 inhabitants, for both sexes[5].Thyroid cancer can occur in all age groups, with an increase in its incidence at the age of 45[6].

Despite being considered one of the least lethal types of cancers, globally there is currently a discussion on thyroid cancer epidemic, related to overdiagnosis – this is attributed to better access to health services, technological changes regarding image diagnostics, frequent biopsies, higher volumes of surgeries, and changes in pathology practices, which detect low-risk non-lethal tumors, promoting overtreatment[7]. However, there is no consensus on overdiagnosis being the real cause of the increase in the number of cases of thyroid cancer[8].

The main type of thyroid cancer is papillary carcinoma, which represents approximately two-thirds of all thyroid cancers in both sexes, followed by follicular thyroid cancer (10-20%), medullary (5-10%), and anaplastic (under 5%) – the latter presents the least favorable prognosis[7]. Definition of the risk factors for follicular, medullary and anaplastic thyroid cancers is much more complex, and the management and prognosis of these histotypes are substantially less favorable than papillary cancers, which could contributed to lower mortality rates[3].

In this context, despite the increase in the incidence of thyroid cancer, mortality rates do not follow the same trend. This fact can be explained, firstly, by detection and early treatment of thyroid cancer, and secondly, by the increase in the detection of papillary carcinoma, which presents better clinical results when compared with the other histotypes of this

cancer, and thirdly, by the standardization of thyroid cancer treatment, which could be another reason for the decrease in the specific mortality of the disease[9,10].

Comprehension of the geographic distribution of thyroid cancer and the behavior of rates throughout time is extremely relevant, as an analysis of the epidemiological situation is necessary to support the planning of public health measures for the most vulnerable groups. These findings can provide information on the possible factors that affect the progression of the disease. To date, there is a scarcity of population-based studies that have examined the epidemiology of thyroid cancer in South America. This study is especially important because it utilizes data from Brazil, a country with continental dimensions and the sixth most populous in the world. The study presented herein has the objective of analyzing the temporal trends for thyroid cancer mortality in Brazil and its geographic regions in the period 2001-2015, and calculate mortality projections for the period 2016-2030.

METHODS

Data sources

An ecological study on temporal series is presented herein, based on secondary data registered in the Mortality Information System (MIS) of the Department of Informatics of the Brazilian Unified Health System (Brazil's publicly funded health care system). Analysis included deaths due to malignant thyroid neoplasms (C73) according to the International Statistical Classification of Diseases and Related Health Problems – 10th review (CID-10), occurred in Brazil in the period 2001-2015, and analyzed according to sex, age group and Brazilian geographic regions.

Data correction

It must be mentioned that, in recent years, the Brazilian MIS has significantly improved its quality, but the utilization of secondary mortality data is still subject to under-registry. Information on the redistribution of deaths per chapter corrected by the Active Search Research[11] was utilized to address the under-registry issue, an initiative of the Ministry of Health, with data available from the Department of Informatics of the Brazilian Unified Health System.

A correction factor for each age group was established[12], as well as for each period, region and sex, from the percentage difference between the amount of deaths notified to MIS and the redistributed deaths, based on Chapter II (neoplasms) of CID-10. The difference was expressed in decimal values, with 1 corresponding to a 100% change (Equation 1). Values higher than 1 could occur, as some locations presented redistributed values above the number of deaths registered by MIS. When the redistributed value was lower than the amount of deaths registered by MIS, a negative difference was obtained.

$$D = (NR - NS) / NS \qquad (1)$$

D is the difference between the redistributed deaths and those registered in MIS (neoplasms) divided by the number of deaths registered in MIS (neoplasms), NR is the number of redistributed deaths (neoplasms), and NS is the number of deaths registered in MIS (neoplasms).

The difference obtained was added to the value 1, yielding the correction factor. The number 1 represents a neutral factor in multiplication, according to Equation 2:

$$F = 1 + D \qquad (2)$$

Where F is the correction factor for Chapter II (neoplasms), and D is the difference between the redistributed deaths and those registered in MIS (neoplasms) divided by the number of deaths registered in MIS (neoplasms).

This factor was multiplied by the number of cancer-related deaths (Equation 3). It was assumed that the correction factor for Chapter II was applicable to thyroid cancer.

$$OC = F \times NOS \qquad (3)$$

Where OC is the corrected number of deaths due to thyroid cancer, NOS is the number of deaths registered in MIS due to thyroid cancer, and F is the correction factor for Chapter II (neoplasms).

Statistics

Standardized mortality rates were calculated with information on the adjusted number of deaths, according to the world population per 100,000 inhabitants. Population data per region, sex and age were obtained from demographic censuses and inter-census projections, available at the webpage of the Brazilian Institute of Geography and Statistics.

Temporal trends for thyroid cancer mortality in Brazil were analyzed, with mortality projections made until 2030 in 5-year periods: 2016-2020, 2021-2025 and 2026-2030.

Analysis of mortality trends was carried out by Joinpoint regression, utilizing theJoinpoint Regression Program (National Cancer Institute, Bethesda, Maryland, USA), version 4.4.0., of January, 2017. The objective of the analysis is to identify the occurrence of possible joinpoints, which are points for which a significant change in trend has occurred. Trend analysis was performed using raw data and corrected data.

The method identified joinpoints based on the model with a maximum of three change points. The final selected model was the most adjusted model, with Annual Percentage Change (APC) based on the trend of each segment, estimating whether these values are statistically significant to a 0.05 level. The significance levels utilized are based on the Monte Carlo permutation model and on the calculation of the annual percentage change of ratio, utilizing the logarithm

of the ratio[13].

When describing trends, the terms “significant increase” or “significant decrease” mean that the slope of trends is statistically significant ($p<0.05$).

Two comparability tests were carried out between the male and female curves, with the objective of comparing two sets of trend data whose average functions are represented by joinpoint regressions. This model tests whether two joinpoint regression functions are identical (coincidence test) or if the two average regression functions are parallel (parallelism tests)[14].

Projections were made for each period utilizing the age-period-cohort model from the Nordpred program (Cancer Registry of Norway, Oslo, Norway), inscribed within statistical program R. Data were compiled in blocks of five years and the limit age group considered for analysis was the first with more than 10 cases for the combined period.

The results of the projections are presented for the total of deaths observed and expected for each period, in Brazil and its five geographic regions. For each period, adjusted mortality rates were calculated on the basis of the world standard population for global comparisons, expressed per 100,000 inhabitants per year (ASW⁄100,000 inhab)[15].

Annual changes were calculated for the number of deaths in the last projected period (2026-2030) compared with the last observed period (2011-2015), where the proportion of the change could occur in terms of changes in risks or demographics (size or structure of the population). These two components can be different from zero and present a positive or negative direction. Calculation can be expressed as[16]:

$$\Delta tot = \Delta risk + \Delta pop = (Nfff - Noff) + (Noff - Nooo) \quad (4)$$

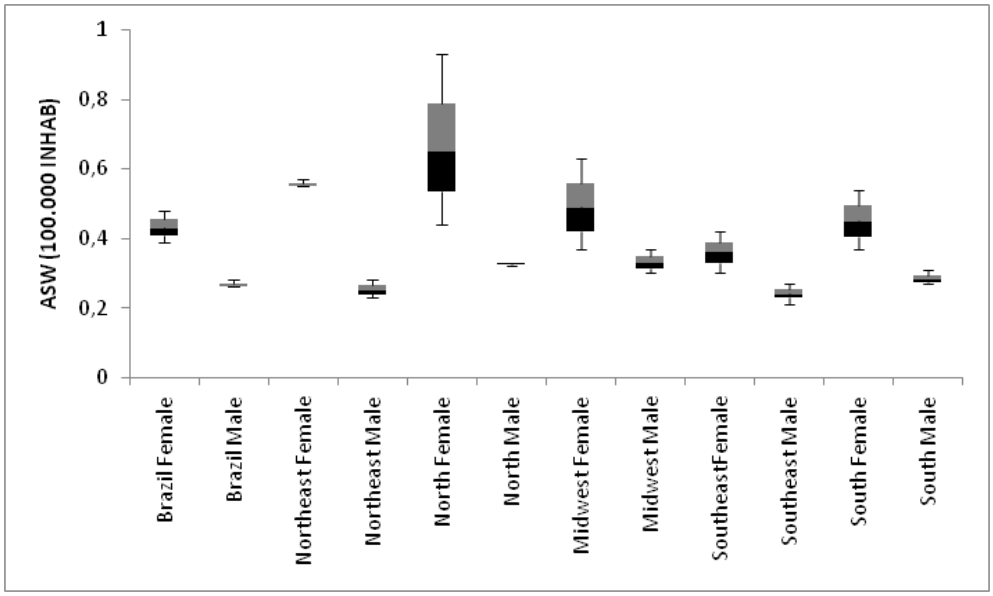
Where Δtot is the total change, Δrisk is the change in function of risk, Δpop is the change in function of the population, Nooo is the number of observed cases, Nfff is the number of projected cases, and Noff is the number of expected cases when the mortality rates increase during the observed period.

RESULTS

In the period 2001-2015, there were 10,057 deaths due to malignant neoplasms of the thyroid gland in Brazil, with 67.2% of deaths affecting females and 32.8% affecting males. The mortality rate standardized to the world population varied between 0.48 to 0.39 deaths/100,000 inhabitants, for women, in 2001 and 2015, respectively. For men, this rate varied between 0.27 and 0.26 deaths/100,000 inhabitants, in 2001 and 2015, respectively. Mortality rates above the Brazilian average were registered in the North, Midwest and South regions, for both sexes. Mortality rates for females must be highlighted for the Northeast region (Figure 1). It was observed that the male/female ratio for thyroid cancer in

the period 2001-2015 was, on average, 1:15. When comparing the curves of males and females in Brazil, no parallelism or coincidence were verified (p<0.001).

Figure 1: Standardized mortality rates for thyroid cancer in Brazil and its geographic regions, according to sex.



Analysis of the historical series of mortality rates for females revealed a significant decreasing trend for Brazil (APC= -1.6% CI95% -2.5;-0.6), Midwest (APC= -3.9% CI95% -7.0;-0.8), Southeast (APC= -2.4% CI95% -3.7;-1.1) and South regions (APC= -2.8% CI95% -4.2;-1.3), with no occurrences of joinpoints for any regions. The trend for female mortality in the North (APC= 0.1%; CI95%: -1.2; 1.5) and Northeast regions (APC= -5.5% CI95% -11.2; 0.6) did not present statistical significance. Male mortality trends were not statistically significant. The trend of male mortality did not show a statistically significant reduction, neither in Brazil considering the regions separately (Table 01).

Table 1: *Temporal trends for mortality due to thyroid cancer in Brazil and Regions using corrected and uncorrected data: number of deaths, APC and Confidence Interval.*

	Uncorrected data		Corrected data	
	Number of deaths	**APC (CI 95%)**	**Number of deaths**	**APC (CI 95%)**
FEMALES				
Brazil	5907	-0.7 (-1,6; 0,2)	6757	-1.6* (-2,5; -0,6)
Northeast	1753	2.4* (0.9; 3.9)	2255	0.1 (-1.2; 1.5)
North	306	-4.3 (-9.8; 1.6)	429	-5.5 (-11.2; 0.6)
Midwest	381	-3.6* (-6.5; -0.5)	417	-3.9* (-7.0; -0.8)
Southeast	2426	-2.0* (-3.3; -0.7)	2677	-2.4* (-3.7; -1.1)
South	1041	-2.5* (-4.0; -1.0)	1110	-2.8* (-4.2; -1.3)

MALES				
Brazil	2818	0.3 (-0.6; 1.2)	3300	-0.5 (-1.5; 0.5)
Northeast	642	3.9* (1.2; 6.6)	851	1.4 (-1.4; 4.3)
North	165	1.8 (-0.8; 4.5)	251	0.3 (-2.2; 2.9)
Midwest	233	-1.5 (-5.7; 2.8)	274	-1.5 (-5.7; 2.8)
Southeast	1226	-1.5 (-3.7; 0.6)	1389	-1.7 (-4.0; 0.5)
South	529	-0.9 (-2.8; 1.0)	569	-1.0 (-2.9; 1.0)

**Statistical significance p < 0.05.*

APC, annual percentage change; 95% CI, 95% confidence interval.

Tables 2 and 3 present the number of deaths and the standardized mortality rates for the observed and projected period, for females and males, respectively. Analysis of overall Brazil data for the 5-year period 2016-2030 provided the projection of 4270 deaths in females due to thyroid cancer. For males, this number was 1907 deaths. Mortality rates for females will present decreases in the future, highlighting the rates of the Midwest, South and North regions, which will present pronounced reductions throughout the period. For males, the same pattern is observed, but the Northeast and North regions will present increasing trends until 2030.

Table 2*: Number of observed and projected deaths in women: age group and ASW / 100,000 inhab.*

	Observed			Projected		
	2001-2005	**2006-2010**	**2011-2015**	**2016-2020**	**2021-2025**	**2026-2030**
BRAZIL						
Age (years)						
0-49	195	197	249	294	335	352
50-74	1059	1107	1272	1494	1811	2201
≥ 75	744	886	1048	1260	1461	1716
ASW	0.45	0.41	0.40	0.40	0.41	0.42
NORTHEAST						
Age (years)						
0-49	83	76	90	94	103	108
50-74	342	382	435	483	552	649
≥ 75	195	296	356	436	504	560
ASW	0.54	0.56	0.55	0.54	0.53	0.52

NORTH						
Age (years)						
0-49	20	18	28	27	31	34
50-74	51	66	86	84	97	114
≥ 75	36	55	63	78	87	96
ASW	0.51	0.56	0.56	0.48	0.44	0.41
MIDWEST						
Age (years)						
0-49	23	16	21	21	24	26
50-74	69	78	81	91	100	112
≥ 75	41	45	50	50	54	66
ASW	0.58	0.48	0.41	0.35	0.31	0.29
SOUTHEAST						
Age (years)						
0-49	60	65	74	83	89	92
50-74	432	407	496	634	817	1019
≥ 75	357	350	435	506	592	724
ASW	0.40	0.32	0.33	0.34	0.36	0.39
SOUTH						
Age (years)						
0-49	25	30	38	35	37	38
50-74	190	190	188	175	179	186
≥ 75	125	155	156	168	175	194
ASW	0.49	0.43	0.37	0.30	0.26	0.24

ASW = age-standardized rate per 100,000 inhabitants (using world standard population).

Table 3: *Number of observed and projected deaths in men: age group and ASW / 100,000 inhab.*

		Observed			Projected	
	2001-2005	**2006-2010**	**2011-2015**	**2016-2020**	**2021-2025**	**2026-2030**
BRAZIL						
Age (years)						
0-49	147	164	170	167	160	157
50-74	555	610	720	819	937	1034
≥ 75	233	319	380	477	576	714
ASW	0.26	0.26	0.26	0.25	0.24	0.23
NORTHEAST						
Age (years)						

0-49	38	48	66	80	95	105
50-74	126	144	194	245	287	326
≥ 75	67	89	89	126	181	247
ASW	0.24	0.26	0.29	0.32	0.34	0.35
NORTH						
Age (years)						
0-49	12	14	18	19	21	22
50-74	40	46	62	95	140	192
≥ 75	10	14	23	30	38	50
ASW	0.30	0.30	0.35	0.42	0.48	0.53
MIDWEST						
Age (years)						
0-49	14	17	10	15	16	17
50-74	44	52	57	69	84	102
≥ 75	18	23	30	47	60	68
ASW	0.36	0.34	0.30	0.32	0.32	0.31
SOUTHEAST						
Age (years)						
0-49	67	59	68	74	79	83
50-74	251	259	289	329	387	448
≥ 75	108	133	181	225	261	306
ASW	0.26	0.23	0.23	0.23	0.22	0.22
SOUTH						
Age (years)						
0-49	19	26	16	22	23	24
50-74	100	115	128	128	133	134
≥ 75	34	61	59	69	78	95
ASW	0.27	0.30	0.25	0.23	0.20	0.19

ASW = age-standardized rate per 100,000 inhabitants (using world standard population).

Figure 02 shows the mortality rates due to thyroid cancer, in the observed and projected periods, according to the influence of the risks and the population structure of Brazil and its regions. For Brazil, there was a percentage change of 66.2% for female mortality rates, explained by the change in the Brazilian demographic structure (69.9%), with a reduced risk of dying from the disease (-2 , 7%). In males, the percentage of change was 50.2% due to changes in the Brazilian demographic structure (66.7%), with a lower risk of dying from the disease (-16.6%).

Figure 2: Comparison between mortality rates (ASW/100,000 inhab) in two periods in Brazil, for both sexes.

DISCUSSION

A significant decreasing trend in female mortality rates for thyroid cancer was verified for Brazil in the period 2001-2015. For males, it was non-significant.There were important regional variations and higher rates for females. When compared with the highest and lowest mortality rates in the world, the thyroid cancer mortality rates for Brazil were considered to be low values, as the USA and Occidental Europe present 0.46 and 0.6 deaths/100,000 inhabitants, respectively[17,18].

Thyroid cancer is more frequent in women. The ratio between sexes (male/female), in general, is 1:4 in developed countries and 1:5 for developing countries. However, in developed countries, mortality rates are between 0.4 and 0.7/100,000 for women and between 0.3 and 0.4/100,000 for men, with a proportion of approximately 1:2[19]. Our results showed that the mortality rates observed for Brazil follow the approximate proportion seen for developed countries.

Despite the increasing incidence trends observed for thyroid cancer in Brazil (APC= 10.0%; CI95%: 7.4;-12.6 for men and APC= 9.2%; CI95%: 6.8- 11.7 for women[20], this increase was mainly due to the increase in the detection of the papillary subtype[21], which presents very good prognosis and contributes to decrease the specific mortality of the disease[22].

This divergence between sexes regarding mortality rates in Brazil can be connected to a predominance of women searching for health assistance, collaborating to early detection and treatment of thyroid cancer, in opposition to the common sense of invulnerability to diseases of men, who present worse prognosis and higher risks of recurrence for this cancer[23, 24].

The patterns and trends for thyroid cancer morality reflect variations in the exposure to risk factors in geographic areas and time periods, and changes in diagnosis and treatment of the disease. In this way, the substantial decline in the prevalence of iodine deficiency in most countries – especially low and intermediate income areas, such as Brazil – can explain the favorable trends for thyroid cancer mortality[3].

The mortality trends for thyroid cancer observed herein are similar to those verified in several parts of the world. In Korea, thyroid cancer presented a reduction, between 2004 and 2015, for women (APC= -4.3%; CI95%: -5.7; -3.0) and men (APC= -4.3%; CI95%: -6.7; -1.8)[9]. In contrast, in the USA, there are increasing trends for thryoid cancer mortality for both sexes (APC= 1.1%; CI95%: 0.6; 1.6)[18].

The decline in mortality reflects high survival, with stability in the long term. Despite the excellent prognosis of small thyroid cancers, many of the patients diagnosed are submitted to extensive treatments, converting over-diagnosis into a public health issue. Patients that are over-diagnosed with thyroid cancer suffer negative effects due to the psychosocial impact of cancer diagnosis, interventions such as partial or total thyroidectomy, ingestion of substitution hormones for the rest of their lives, monitoring,surgical complications andother adverse effects, besides social and financial damages[25].

In Brazil, the distribution of hierarchical care levels for cancer patients is unequal, with pronounced disparity

between areas that count with better urban structures (Southeast and South regions), which present well-equipped health services that are well distributed in the territory, in opposition to those geographic regions that lack intermediate hierarchical levels for cancer assistance (North and Northeast regions)[26]. This specific situation can explain the inequalities observed in the mortality rates for the different Brazilian geographic regions, with stable trends for the poorest regions of the country, for the female sex, in contrast with the decreasing trends verified for the remaining regions.

The projection model for Brazil estimates that, in 2026-2030, thyroid cancer will be responsible for 4270 deaths in females and 1907 deaths in males. Other countries have already demonstrated similar behavior for this cancer in the future. In the USA, mortality projections for thyroid cancer indicate that, in 2030, thyroid cancer will cause 2000 deaths, in men and women, with an incidence of 183,000 cancer cases[27].Projections made in Germany estimate that in 2030 there will be 259 deaths in men and 232 deaths in women due to thyroid cancer, in opposition with high incidence, becoming the tenth most frequent cancer in the country[28].

This profile for thyroid cancer, with decreasing mortality and drastic increase in incidence, leads to the hypothesis that there is no epidemic, but an increase in diagnosis, where treatment is mostly curative. In the next decades, it is necessary to increase efforts in the stratification of risks to ensure an appropriate therapeutic response, aimed at identification and cure of the few patients whose disease is susceptible to shorten their lives[27]. Despite the fact that Brazil counts with a universal coverage healthcare system, the challenge for the next years will be the development of a system capable of responding to changes in health risks and of assisting Brazilian due to the demographic changes experienced by the country.

Regarding death registry in Brazil, it should be mentioned that in the past there were issues with data reliability, especially in the North and Northeast regions. However, quality improvements and advances in the mortality information system have been implemented since year 2000. Cancer projections must be analyzed taking into consideration the current conditions of diagnosis and treatment, which can be altered in the future and, consequently, change mortality trends.

CONCLUSIONS

Thyroid cancer mortality in Brazil presents a significant decreasing trend for women and stability for men. Projections until 2030 demonstrate that mortality rates should continue to present this decreasing behavior. The most significant aspects are the regional differences for thyroid cancer mortality, as the poorest regions of Brazil present higher rates, while the South and Southeast regions are the most developed and therefore present lower rates. This discrepancy should continue until 2030. Given the description of this Brazilian scenario, with decreasing mortality rates, health policies

should focus on improving access to health services, at least in the developed regions of the country. The poorest regions of the country, which had a high projection of rates, such as the North and Northeast, should look for ways to minimize some risk factors for thyroid cancer, such as promoting improved access to health services for the population. From this, it is possible to prevent and stimulate a healthy diet (with the correct amount of iodine), accompany individuals with a family history of thyroid cancer and a history of excessive use of radiation, as well as encourage healthy lifestyle habits. Therefore, these actions can control the incidence of the disease and minimize overdiagnosis.

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