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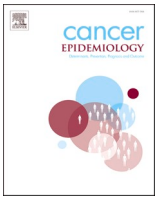

Temporal trends and factors associated with the cancer diagnosed at stage IV in patients included in the integrated hospital-based cancer registry system in Brazil in two decades

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ABSTRACT

Background: In several countries, such as Brazil, the oncological diagnosis usually occurs at an advanced stage of the disease. Thus, the aim of this study was to investigate temporal trends and factors associated with the cancer diagnosed at stage IV in Brazil in two decades.
Methods: Secondary-based study, with time series analysis for trend assessment and cross-sectional of factors associated with diagnosis of female breast, prostate, cervix uteri, colorectal, lung, stomach, lip and oral cavity, thyroid, esophagus or corpus uteri at stage IV.
Results: 1,218,322 cases were evaluated. The types of cancer with the highest proportion of stage IV at diagnosis in men and women, respectively, were: lung (53.7% and 57.4%), stomach (48.4% and 45.0%) and lip/oral cavity (53.5% and 43.4%). Most showed an increasing trend of annual percent change of cancer diagnosed at stage IV, being more pronounced in corpus uteri cancer (2013–2019: +7.4%, $p < 0.001$). The odds of cancer diagnosed at stage IV were associated with different factors, according to primary tumor site, but marked by the inverse association with female sex [odds ratio (OR) ranging from 0.42 to 0.91, $p < 0.001$] and direct association in cases with < 7 years of study (OR ranging from 1.08 to 1.81, $p < 0.001$), living without a partner (OR ranging from 1.06, $p < 0.050$ to1.27, $p < 0.001$), living in the South and Southeast regions (OR ranging from 1.04 to 1.13, $p < 0.001$), with more than one tumor (OR ranging from 1.19, $p < 0.050$ to 1.54, $p < 0.001$) and treated in Centers of High Complexity in Oncology (OR ranging from 1.03, $p < 0.050$ to1.24, $p < 0.001$).
Conclusion: There was a high frequency of cancer diagnosed at stage IV and an increasing trend in different cancer types, which were associated with distinct sociodemographic, lifestyle, and clinical factors.

1. Introduction

With increasing incidence, cancer is a public health problem and represents the second leading cause of death worldwide [1]. In 2020, there were about 19.3 million new cases, and its global incidence is estimated to reach 28.4 million in 2040. The magnitude of this increase will be most notable in countries with low (95.0%) and medium (64.0%) Human Development Index (HDI) [2]. In Brazil, the forecast for each year of the triennium 2020–2022 is that there will be about 625 thousand new cases [3].

In several countries, such as Brazil, the oncological diagnosis usually occurs at an advanced stage of the disease, and this epidemiological pattern is influenced by exposure to modifiable and non-modifiable risk factors, among which the barriers related to health services (difficult access, insufficient coverage of screening programs, and delays in diagnosis), as well as socioeconomic, cultural, and demographic inequities [4–8]. Late diagnosis leads to higher morbidity and mortality [9], reaffirming the importance of early identification of the disease, reduction of delay in diagnosis and, consequently, the reduction of unfavorable outcomes.

Particularly in relation to cases of cancer diagnosed at stage IV, its magnitude is known to be expressive and variable according to the

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primary tumor site [10–14]. Although analyzes of big data, such as the Integrator Module of Hospital Cancer Registries (HCR), can generate solid information on the clinical staging of the disease at diagnosis, the scientific literature lacks products from robust analyses of temporal trends and factors related to diagnosis at this stage of the disease to support the planning and readjustment of public health policies for cancer control in the country. Thus, the aim of the present study is to investigate the temporal trend and factors associated with the cancer diagnosed at stage IV in patients included in the integrated hospital-based cancer registry system in Brazil over two decades.

2. Methods

This is a secondary-based study comprising a time series analysis to assess trends and a cross-sectional study to identify factors associated with the cancer diagnosed at stage IV. Data from two decades (2000–2019) were used, obtained on June 10, 2021, from the Integrator Module of HCR (http://www.inca.gov.br), a data tabulator coordinated by the Brazilian National Cancer Institute (INCA), which includes cases from hospital-based cancer in the 26 Brazilian states and the Federal District. A thematic Brazilian map with the HCR by states was designed in ArcGIS 10.5 software.

Permission for access and use of the information was not required, as they are secondary data and in the public domain, according to Resolution 510/2016 of the National Health Council.

2.1. Eligibility Criteria

Cases of both sexes were included, diagnosed with one of the ten types of cancer with the highest incidence in the Integrator Module of HCR, in the period of interest, namely: 1st) female breast (C50), 2nd) prostate (C61), 3rd) cervix uteri (C53), 4th) colorectal (C18–21), 5th) lung (C33–34), 6th) stomach (C16), 7th) lip and oral cavity (C00–06), 8th) esophagus (C15), 9th) thyroid (C73) or 10th) corpus uteri (C54–55). The cases were selected based on topographical codes described on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [15]. To minimize the inclusion of duplicate records, only analytical cases (diagnosed and treated in the same hospital unit) were considered. Cases with patients younger than 18 years old and with incomplete data on clinical staging were excluded.

2.2. Dependent variable

For the purposes of registration at the HCR, the clinical staging data of the tumor recorded in the medical record by the doctor referring to the patient's first appointment or within two months of diagnosis is used. There is a specific classification for each type of cancer, whose staging varies from I to IV, defined by the Classification of Malignant Tumors (TNM) [16]. The cancer diagnosed at stage IV, the most advanced form of the disease, was considered the dependent variable of this study.

2.3. Independent variables

The following were evaluated: age group (<60 vs. ≥60 years); sex (male vs. female); self-reported skin color according to the National Census Bureau—IBGE [whites vs. non-white (black, Asian, brown and indigenous)]; study time (<7 vs. >7 years), marital status [living with a partner (married or in a stable relationship) vs. no partner (widowed, divorced or single)]; region of residence categorized according to the HDI of the year 2000 (http://www.atlasbrasil.org.br) (North, Northeast and Midwest vs. South and Southeast) and habitual use of tobacco (no vs. yes). According to what is recommended in the HCR, the assessment of habitual use of tobacco considers the use in the patient's entire life and the occasional smoker was considered a non-smoker.

In addition, referral made by the National Health System, the Sistema Único de Saúde (SUS), for cancer treatment (no vs. yes); presence of more than one primary tumor (no vs. yes); and treatment in High Complexity Oncology Centers (CACON) (no vs. yes) was assessed.

CACON is understood to be the hospital that has the technical conditions, physical facilities, equipment and human resources suitable for the provision of highly complex specialized care for the definitive diagnosis and treatment of all types of cancer [17].

2.4. Statistical analysis

Descriptive and logistic regression analyses were performed using Stata Data Analysis and Statistical Software 13.1. Joinpoint 4.9 software was used for temporal trend analysis. A p-value< 0.05 was considered statistically significant.

Descriptive analyses of the independent variables were performed, expressed in absolute and relative numbers, according to the type of cancer. Data on clinical staging at diagnosis were presented as absolute and relative numbers and represented by graphical analyses.

Time trend analyses were performed, for each tumor type and sex, through estimates of the annual percent change (APC) and 95% confidence intervals (95% CI) of cancer diagnosed at stage IV, over time (variable independent), from the Joinpoint regression model. For the adjustment of the model, junction points from 0 to 3 (trends indicated by straight line segments) were admitted. For the interpretation of trends, the non-statistical significance characterized a stable APC. The statistically significant APC, when positive, indicated an increasing trend and, when negative, a decreasing trend [18].

Then, univariates logistics regressions analyses were performed, using the odds ratios (OR) with 95% CI as estimator, to verify the associations between each type of cancer diagnosed at stage IV and the independent variables. All variables with $p < 0.20$ were tested in the multiple models [19], with a forward stepwise selection method. This procedure resulted in 10 multiple models with different adjustment variables. Variables with $p < 0.05$ were kept in the models. The missing data for independent variables were considered as an extra class in the multivariate analyses. Those with OR values less than one were considered as an inverse association and those with OR were greater than unity as a direct association with the cancer diagnosed at stage IV.

3. Results

HCRs were observed in all regions of the country, and the most were concentrated in states of the southern and southeastern, mainly in São Paulo state (Fig. S1). The incompleteness of clinical staging data ranged from 19.2% to 40.1%, according to tumor type (Table S1). Thus, 1,218,322 cancer cases with these complete data were included (Fig. S2).

Among the analyzed cases, the majority were < 60 years old (58.6%), female (59.8%), < 7 years of schooling (41.8%) and residing in the South and Southeast regions (72.4%). The variables with the highest percentage of missing data were smoking (57.3%), referral by SUS (45.4%), marital status (44.5%), skin color (43.1%) and having more than one primary tumor (41.0%) (Table S2). The tumor sites with the highest frequency of stage IV at diagnosis in men and women, were respectively: lung (53.7% and 57.4%), stomach (48.4% and 45.0%), and lip and oral cavity (53.5% and 43.2%) (Fig. 1).

Most tumor types showed an increasing trend of APCs of stage IV at diagnosis, whose greatest growth occurred in corpus uteri cancer (2013–2019: +7.4%, $p < 0.001$). The APCs of cases of cervix uteri cancer (2000–2019: +4.8%, $p < 0.001$), colorectal (female sex 2000–2019: +1.2%, $p < 0.001$) and lung (female sex 2000–2012: +2.7%, $p < 0.001$/ 2012–2019: +1.4%, $p = 0.030$; male 2000–2009: +1.6%, $p = 0.002$ and 2012–2019: +1.2%, $p = 0.023$) diagnosed at stage IV maintained an increasing trend throughout the time course. There was an initial retraction, with a subsequent increase in APC of

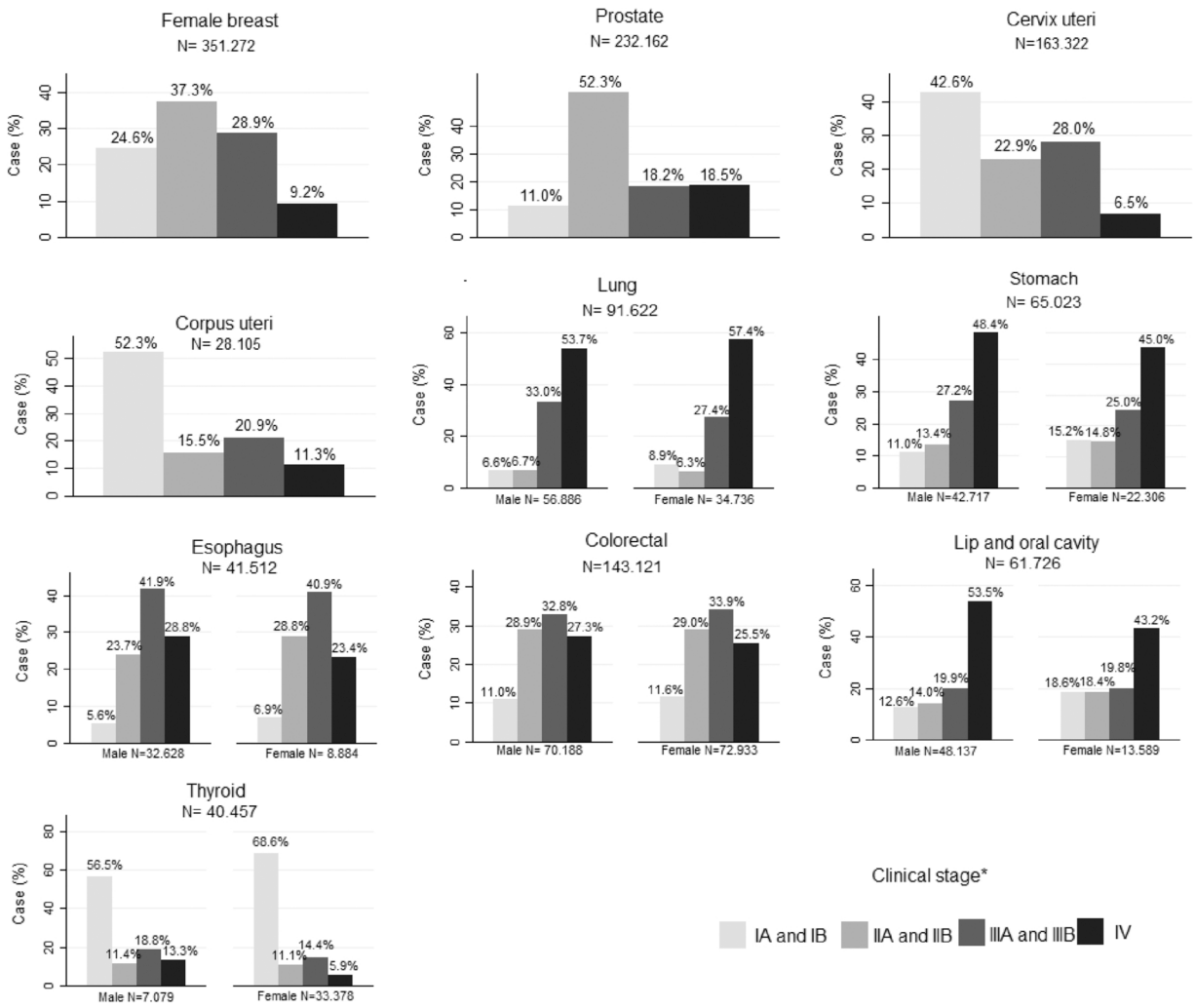

Fig. 1. Clinical stage at diagnosis of different types of cancer in patients included in the integrated hospital-based cancer registry system in Brazil from 2000–2019.
Note: N = number of observations. * Defined by the Classification of Malignant Tumors [16].

stage IV at diagnosis in female breast cancer (2000–2003: −11.8%, $p = 0.003$ and 2013–2019: +3.3%, $p = 0.004$) and prostate (2000–2012: −5.4%, $p < 0.001$ and 2012–2017: +5.6%, $p < 0.001$) (Fig. 2 and Table 1).

Some independent variables were associated in different ways with the stage IV at diagnosis, according to the type of cancer (Fig. 3). Age ≥ 60 years was associated with stage IV at diagnosis of all tumor types, with an inverse association in colorectal, lung, stomach, lip and oral cavity and thyroid cancer (OR ranging from 0.70 to 0.83, $p < 0.001$); and direct in the other cases (OR ranging from 1.10 to 3.99, $p < 0.001$). Female sex was directly associated with stage IV at diagnosis of lung cancer (OR= 1.11, 95% CI: 1.08–1.14) and inversely associated in most other cases (OR ranging from 0.42 to 0.91, $p < 0.001$). Non-white skin color was inversely associated with stage IV at diagnosis of prostate cancer (OR= 0.83, 95% CI: 0.80–0.85) and cervix uteri (OR= 0.88, 95% CI: 0.84–0.94) and directly associated with stage IV at diagnosis of breast cancer (OR= 1.09, 95% CI: 1.05–1.12) and lip and oral cavity (OR= 1.25, 95% CI: 1.17–1.41). Study time < 7 years was inversely associated with stage IV at diagnosis of colorectal (OR= 0.93, 95% CI: 0.91–0.96) and lung (OR= 0.89, 95% CI: 0.86–0.91) cancer and directly associated in most other cases (OR ranging from 1.08 to 1.81, $p < 0.001$). Not living with a partner was directly associated with stage IV at diagnosis of most types of cancer (OR ranging from 1.06, $p < 0.050$ to 1.27, $p < 0.001$) (Tables 2 and 3).

Living in the South and Southeast regions was inversely associated with stage IV at diagnosis in prostate (OR= 0.68, 95% CI: 0.67–0.70) and lung (OR= 0.91, 95% CI: 0.88–0.95) and directly associated in most other cases (OR ranging from 1.04 to 1.13, $p < 0.001$). Smoking was directly associated with stage IV at diagnosis of breast, prostate, lung, lip and oral cavity and esophagus cancer (OR ranging from 1.05, $p < 0.050$ to 1.76, $p < 0.001$). Having more than one primary tumor was directly associated with stage IV at diagnosis of most tumor types (OR ranging from 1.19, $p < 0.050$ to 1.54, $p < 0.001$). The referral made by the SUS for cancer treatment was directly associated with stage IV at diagnosis of breast, colorectal, esophagus, and corpus uteri cancer (OR ranging from 1.12 to 1.32, $p < 0.001$). The treatment performed in a CACON showed an inverse association with stage IV at diagnosis in prostate cancer (OR= 0.91; 95% CI: 0.89–0.93) and esophagus (OR= 0.85; 95% CI: 0.78–0.93) and a direct association in most other cases (OR ranging from 1.03, $p < 0.050$ to 1.24, $p < 0.001$) (Tables 2 and 3).

4. Discussion

This study is pioneer in encompassing different tumor sites to analyze the temporal trend and factors associated with cancer diagnosed at stage IV in Brazil. It was observed that cases of lung, stomach, and lip and oral cavity neoplasms had a higher frequency of stage IV at diagnosis and that there was a predominance of an increasing trend of this outcome, especially in corpus uteri cancer. Several variables were associated with stage IV at diagnosis, the inverse association being more

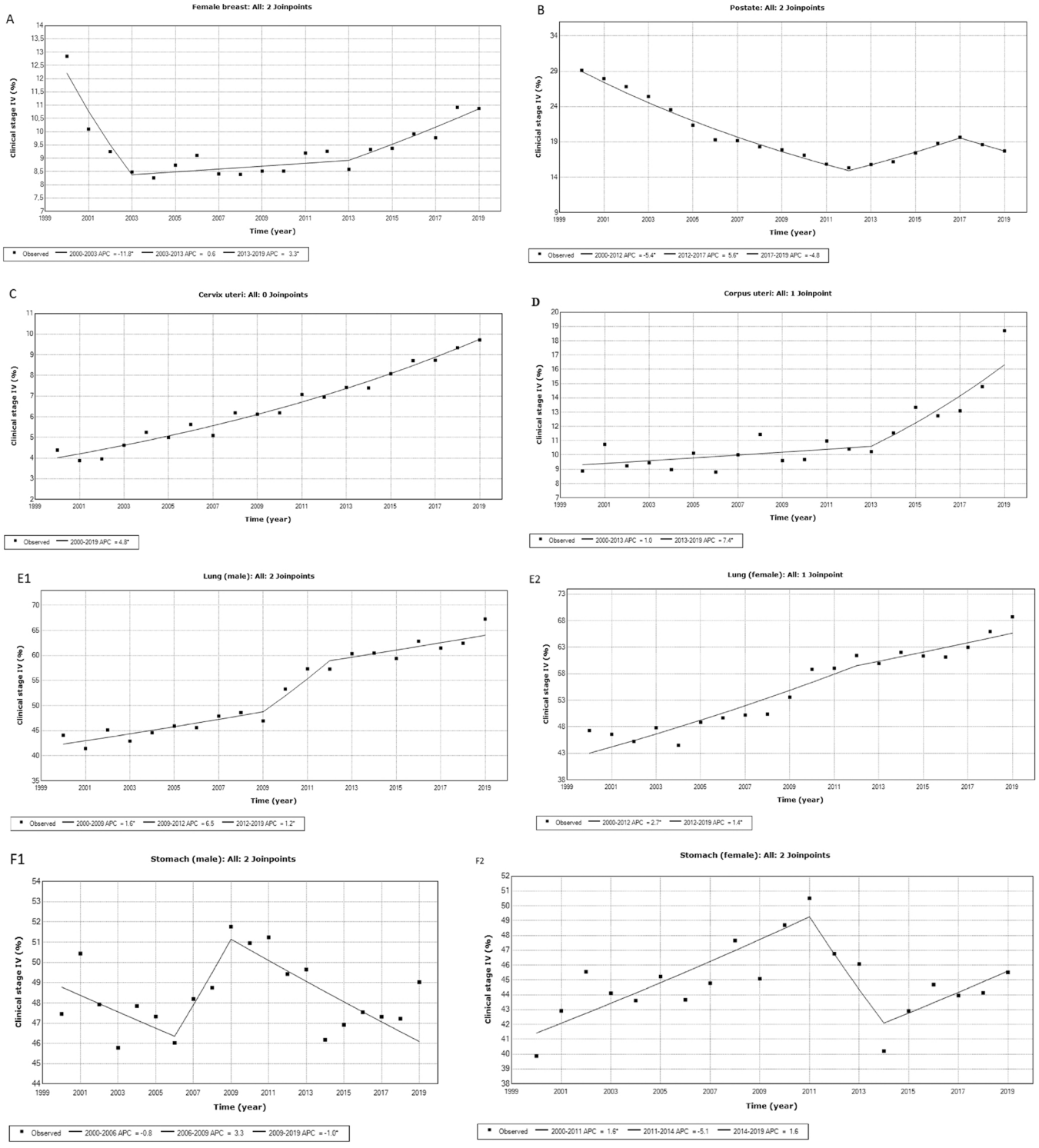

Fig. 2. Time trend in the diagnosis of different types of cancer diagnosed in the stage IV in patients included in the integrated hospital-based cancer registry system in Brazil from 2000-2019. **Note:** APC= annual percent change. *Indicates that the APC is statistically significant with an alpha error of 0.05.

frequent with females and direct association more frequent with lower education, absence of a partner, residing in the South and Southeast regions of the country, having more than one primary tumor and being treated in CACON.

According to the general cancer incidence estimate for 2020 in Brazil, except non-melanoma skin cancer, the most frequent neoplasms in men are prostate (29.2%), colorectal (9.1%), lung (7.9%), stomach (5.9%), oral cavity (5.0%), esophagus (3.9%), bladder (3.4%), non-Hodgkin's lymphoma (2.9%), larynx (2.9%) and leukemia (2.6%); and in women they are breast (29.7%), colorectal (9.2%), cervix uteri (7.5%), lung (5.6%), thyroid (5.4%), stomach (3.5%), ovary (3.0%), corpus uteri cancer (2.9%), non-Hodgkin's lymphoma (2.4%) and central nervous system (2.3%) [3]. However, this estimate does not consider clinical staging at diagnosis. There is little evidence about cancer

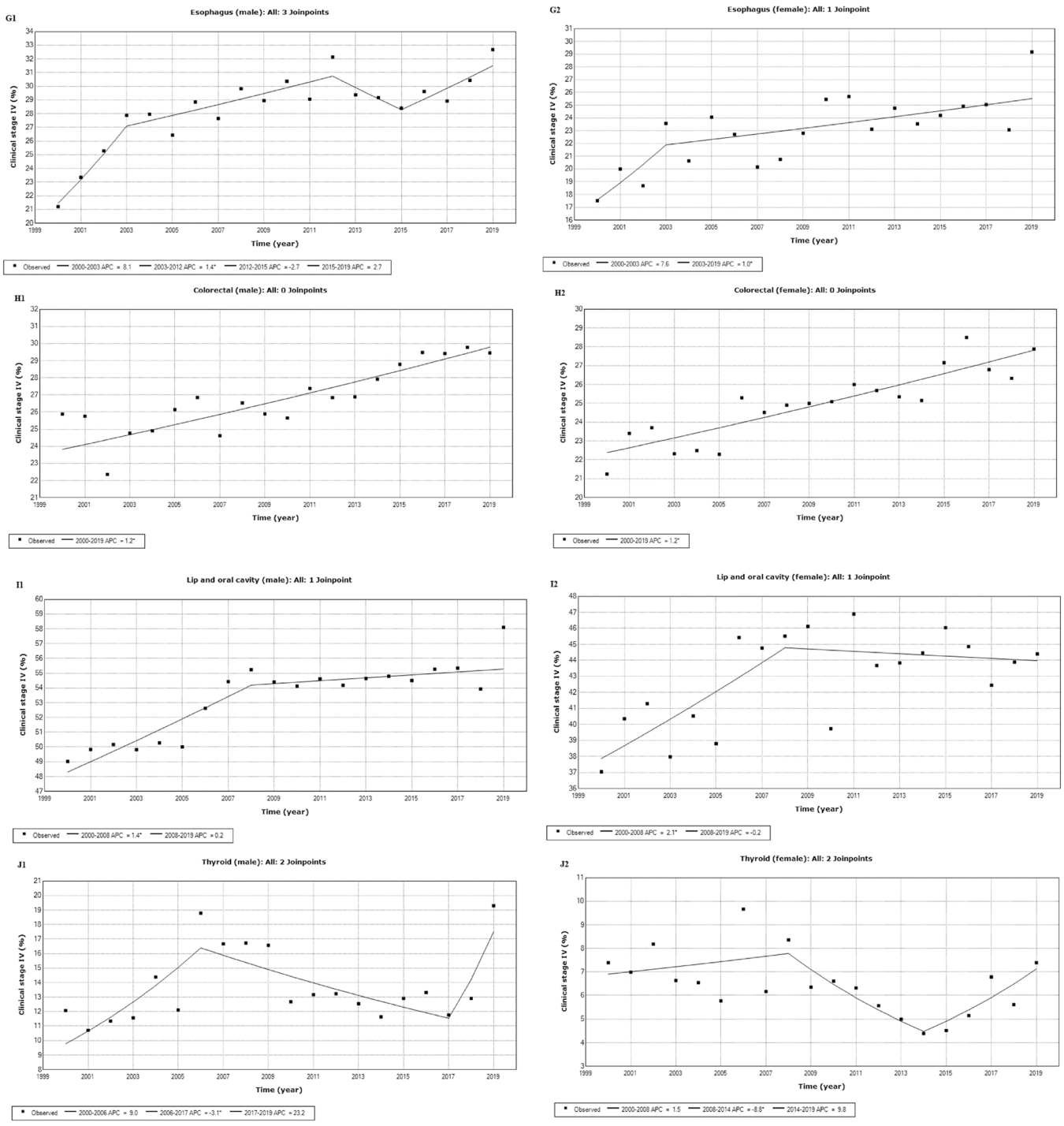

Fig. 2. (*continued*).

diagnosed at stage IV in Brazil, which limits our discussions.

Probably, a portion of cancer deaths would have been avoided if part of the 254,388 cases diagnosed at stage IV were identified earlier, suggesting a potential benefit of investing in promoting early diagnosis. Corroborating the results regarding the high frequency of cancer diagnosed at stage IV, previous work with HCR data from 2000-2014 showed high percentages of stage IV at diagnosis of tongue cancer (41.0%), non-oral cancer tongue (54.1%) and tongue and tongue tonsil cancer (70.2%) [12]. Other HCR data from 2008 to 2014 showed high frequencies of stage IV at diagnosis of stomach (56.4–77.0%) and lung cancer (65.9–82.4%) [13].

We assume that, in addition to the cross-sectional description of the frequencies of cancer diagnosed at stage IV, the analysis of temporal trends is especially relevant. Most tumor types were marked by an increasing trend of APC, suggesting that no changes that raised hypotheses about the positive effects of the Oncology Care National Policy in early diagnosis were identified [20].

In contrast to the fact that it is not one of the neoplasms with the highest percentage of stage IV at diagnosis, the highest growth of APC (2013–2019: +7.4%, $p < 0.001$) occurred in corpus uteri cancer. Among the restricted national studies, there is one carried out at the São Paulo State Cancer Institute (ICESP), with data from 2008-2018, in which

Table 1
Temporal trend in the diagnosis of cancer diagnosed in the stage IV in patients included in the integrated hospital-based cancer registry system in Brazil from 2000-2019.

Anatomical region	Type of cancer	Segment	Lower Endpoint	Upper Endpoint	APC (CI 95%) (%)	Test (t)	Prob >|t|*
Breast	Female breast	1	2000	2003	-11.8 (−18.1; −5.0)	-3.7	**0.003**
		2	2003	2013	+0.6 (−0.5; +1.8)	+1.2	0.245
		3	2013	2019	+3.3 (+1.3; +5.4)	+3.6	**0.004**
Gender related	Prostate	1	2000	2012	-5.4 (−6.0; −4.8)	-19.7	**<0.001**
		2	2012	2017	+5.6 (+3.0; +8.2)	+4.8	**<0.001**
		3	2017	2019	-4.8 (−16.1; +7.9)	-0.9	0.406
	Cervix uteri	1	2000	2019	+4.8 (+4.3; +5.3)	+22.9	**<0.001**
	Corpus uteri	1	2000	2013	+1.0 (−0.5; +2.5)	+1.5	0.166
		2	2013	2019	+7.4 (+3.8; +11.2)	+4.5	**<0.001**
Respiratory	Lung						
	Male	1	2000	2009	+1.6 (+0.7; +2.5)	+4.0	**0.002**
		2	2009	2012	+6.5 (−0.6; +14.1)	+2.0	0.068
		3	2012	2019	+1.2 (+0.2; +2.2)	+2.6	**0.023**
	Female	1	2000	2012	+2.7 (+2.0; +3.5)	+7.5	**<0.001**
		2	2012	2019	+1.4 (+0.2; +2.7)	+2.4	**0.030**
Upper digestive tract	Stomach						
	Male	1	2000	2006	-0.8 (−2.7; +1.1)	-1.0	0.354
		2	2006	2009	+3.3 (−5.5; +13.0)	+0.8	0.438
		3	2009	2019	-1.0 (−1.7; −0.4)	-3.4	**0.005**
	Female	1	2000	2011	+1.6 (+0.9; +2.3)	+5.1	**<0.001**
		2	2011	2014	-5.1 (−11.4; +1.7)	-1.7	0.125
		3	2014	2019	+1.6 (−0.4; +3.6)	+1.8	0.102
	Esophagus						
	Male	1	2000	2003	+8.1 (−0.2; +17.1)	+2.2	0.055
		2	2003	2012	+1.4 (+0.3; +2.6)	+2.8	**0.021**
		3	2012	2015	-2.7 (−10.8; +6.1)	-0.7	0.490
		4	2015	2019	+2.7 (−0.8; +6.4)	+1.8	0.113
	Female	1	2000	2003	+7.6 (−9.3; +27.6)	+0.9	0.375
		2	2003	2019	+1.0 (+0.1; +1.8)	+2.4	**0.030**
Lower digestive tract	Colorectal						
	Male	1	2000	2019	+1.2 (+1.0; +1.6)	+8.9	**<0.001**
	Female	1	2000	2019	+1.2 (+0.8; +1.5)	+7.0	**<0.001**
Lip and oral cavity	Lip and oral cavity						
	Male	1	2000	2008	+1.4 (+0.8; +2.1)	+5.1	**<0.001**
		2	2008	2019	+0.2 (−0.2; +0.5)	+1.2	0.268
	Female	1	2000	2008	+2.1 (+0.2; +4.1)	+2.3	**0.034**
		2	2008	2019	-0.2 (−1.2; +0.9)	-0.3	0.743
Thyroid	Thyroid						
	Male	1	2000	2006	+9.0 (−0.5; +19.4)	+2.1	0.061
		2	2006	2017	-3.1 (−5.1; −1.2)	-3.5	**0.005**
		3	2017	2019	+23.2 (−14.8; +78.1)	+1.2	0.242
	Female	1	2000	2008	+1.5 (−5.0; +8.5)	+0.5	0.633
		2	2008	2014	-8.8 (−15.7; −1.4)	-2.6	**0.024**
		3	2014	2019	+9.8 (−0.8; +21.5)	+2.0	0.069

Note: APC= annual percent change; CI= confidence interval.
*Are highlighted in bold p-values with alpha error < 0.050.

Fig. 3. Factors associated with the cancer diagnosed in the stage IV in patients included in the integrated hospital-based cancer registry system in Brazil from 2000-2019. **Note:** SUS= Sistema Único de Saúde (National Health System); CACON= High Complexity in Oncology Centers. [a] black, asian, brown and indigenous; [b] widowed, divorced or single.

Table 2
Factors associated with the female breast, prostate, cervix uteri, corpus uteri and lung cancer diagnosed in the stage IV in patients included in the integrated hospital-based cancer registry system in Brazil from 2000-2019.

Variables	Female breast		Gender related						Respiratory	
			Prostate		Cervix uteri		Corpus uteri		Lung	
	Univariate	Multivariate[a]	Univariate	Multivariate[b]	Univariate	Multivariate[c]	Univariate	Multivariate[d]	Univariate	Multivariate[e]
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Age groups (years)				a						
<60	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>60	1.12(1.09;1.18)[f]	1.10(1.06;1.14)[f]	1.36(1.30;1.39)[f]	1.27 (1.22;1.31)[f]	1.52(1.48;1.60)[f]	1.50(1.46;1.57)[f]	1.19(1.11;1.26)[f]	1.16(1.10;1.22)[f]	0.81(0.77;0.85)[f]	0.80(0.77;0.83)[f]
Sex										
Male	–	–	–	–	–	–	–	–	1.00	1.00
Female	–	–	–	–	–	–	–	–	1.16(1.13;1.19)[f]	1.11(1.08;1.14)[f]
Race/ skin color										
White	1.00	1.00	1.00	1.00	1.00	1.00	1.00	–	1.00	–
Non-white[g]	1.13(1.10;1.17)[f]	1.09(1.05;1.12)[f]	0.96 (0.93;0.98)[h]	0.83 (0.80;0.85)[f]	0.83(0.79;0.87)[f]	0.88(0.84;0.94)[f]	1.08(0.97;1.19)	–	1.08(1.04;1.12)[f]	–
Missing data	1.06 (1.03;1.09)[h]	1.07 (0.99;1.14)	0.74(0.72;0.76)[f]	0.78 (0.74;0.81)[f]	1.03(0.97;1.08)	0.98(0.93;1.06)	1.02(0.93;1.11)	–	1.11(1.08;1.15)[f]	–
Years of study										
<7	1.28(1.24;1.31)[f]	1.23(1.20;1.26)[f]	1.32(1.28;1.35)[f]	1.24 (1.21;1.27)[f]	1.11(1.06;1.16)[f]	1.08 (1.03;1.14)[h]	1.05(0.96;1.14)	–	0.88(0.85;0.91)[f]	0.89(0.86;0.91)[f]
>7	1.00	1.00	1.00	1.00	1.00	1.00	1.00	–	1.00	1.00
Missing data	1.12(1.09;1.16)[f]	1.10(1.07;1.14)[f]	1.23(1.19;1.27)[f]	1.17 (1.14;1.21)[f]	1.06(0.99;1.12)	0.99(0.94;1.05)	0.87(0.79;1.02)	–	0.92(0.89;0.96)[f]	0.94 (0.91;0.98)[h]
Marital status										
With partner[i]	1.00	1.00	1.00	1.00	1.00	–	1.00	1.00	1.00	1.00
Without partner[j]	1.28(1.24;1.32)[f]	1.27(1.24;1.32)[f]	1.12(1.08;1.17)[f]	1.11 (1.07;1.16)[f]	0.98(0.93;1.04)	–	1.28(1.14;1.44)[f]	1.21(1.07;1.37)[f]	1.15(1.09;1.21)[f]	1.08 (1.03;1.14)[h]
Missing data	1.06(1.03;1.08)[f]	1.00(0.99;1.13)	1.02 (1.01;1.08)[h]	1.01(0.99;1.22)	1.24(0.98;1.30)	–	1.07(0.98;1.15)	0.89 (0.74;1.07)	1.10 (1.07;1.13)[h]	1.04(0.99;1.09)
Region of residence										
North, Northeast and Midwest	1.00	–	1.00	1.00	1.00	1.00	1.00	–	1.00	1.00
South and Southeast	1.01(0.98;1.03)	–	0.69(0.68;0.71)[f]	0.68 (0.67;0.71)[f]	1.26(1.21;1.31)[f]	1.13(1.08;1.20)[f]	1.04(0.94;1.13)	–	0.91 (0.88;0.94)[h]	0.91(0.88;0.95)[f]
Missing data	1.43(0.84;1.56)	–	0.58(0.48;0.70)[f]	0.52 (0.43;0.63)[f]	1.30(0.92;1.84)	1.18(0.83;1.67)	0.35(0.13;1.05)	–	0.69(0.56;1.02)	0.68(0.55;1.04)
Current smoking										
No	1.00	1.00	1.00	1.00	1.00	–	1.00	–	1.00	1.00
Yes	1.06 (1.02;1.11)[h]	1.05 (1.01;1.09)[h]	1.19(1.14;1.23)[f]	1.18 (1.15;1.24)[f]	0.97(0.91;1.04)	–	1.01(0.86;1.20)	–	1.19(1.16;1.21)[f]	1.18(1.05;1.21)[f]
Missing data	1.07 (1.04;1.10)[h]	1.08(0.98;1.10)	0.97(0.94;1.12)	0.98(0.84;1.20)	1.07(0.92;1.11)	–	0.99(0.92;1.08)	–	1.08 (1.05;1.09)[h]	0.98(0.96;1.15)
More than one primary tumor										
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	–	1.00	–
Yes	1.41(1.33;1.52)[f]	1.40(1.35;1.44)[f]	1.45(1.33;1.57)[f]	1.44 (1.33;1.56)[f]	1.65(1.40;1.95)[f]	1.54(1.30;1.82)[f]	1.21(0.96;1.52)	–	1.08(0.99;1.18)	–
Missing data	1.01(0.99;1.03)	1.01(0.94;1.10)	0.76(0.75; 1.11)	0.85(0.80;1.03)	1.27 (1.22;1.32)[h]	1.31(1.21;1.43)[f]	0.99(0.92;1.08)	–	1.12 (1.09;1.15)[h]	–
Referenced by SUS										
No	1.00	1.00	1.00	–	1.00	–	1.00	1.00	1.00	–
Yes	1.32(1.28;1.38)[f]	1.30(1.25;1.35)[f]	0.99(0.95;1.02)	–	1.05(0.99;1.12)	–	1.20 (1.05;1.35)[h]	1.19 (1.05;1.33)[h]	0.99 (0.94;1.03)	–
Missing data	1.23(1.18;1.27)[f]	1.12 (1.05;1.20)[h]	0.82(0.79;1.05)	–	1.29(0.98;1.38)	–	1.19 (1.05;1.35)[h]	1.23 (1.13;1.38)[h]	1.05 (0.99;1.10)	–

(*continued on next page*)

Table 2 (*continued*)

Variables	Female breast		Gender related						Respiratory	
			Prostate		Cervix uteri		Corpus uteri		Lung	
	Univariate	Multivariate[a]	Univariate	Multivariate[b]	Univariate	Multivariate[c]	Univariate	Multivariate[d]	Univariate	Multivariate[e]
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Treatment in CACON										
No	1.00	1.00	1.00	1.00	1.00	–	1.00	–	1.00	–
Yes	1.04(1.02;1.07)[f]	1.03 (1.01;1.06)[h]	0.93 (0.91;0.94)[h]	0.91 (0.89;0.93)[f]	0.99(0.95;1.03)	–	0.94(0.88;1.02)	–	1.04 (1.01;1.07)[h]	–
Missing data	1.55(1.23;1.96)[f]	1.57(1.25;1.98)[f]	1.03(0.85;1.26)	0.96(0.79;1.17)	0.98(0.96;1.10)	–	0.90(0.32;2.54)	–	1.75 (1.19;1.22)[h]	–

Note: OR= odds ratio; CI= confidence interval; SUS= Sistema Único de Saúde (National Health System); CACON= High Complexity Oncology Centers.

[a] age groups, race/ skin color, years of study, marital status, current smoking, more than one primary tumor, referred by SUS, treatment in CACON;

[b] age groups, race/skin color, years of study, marital status, geographic regions, current smoking, more than one primary tumor, treatment in CACON;

[c] age groups, race/skin color, years of study, geographic regions, more than one primary tumor, referred by SUS, treatment in CACON;

[d] age groups, sex, race/ skin color, marital status, more than one primary tumor, Referenced by SUS and treatment in CACON.

[e] age groups, sex, race/skin color, years of study, marital status, geographic regions, current smoking, more than one primary tumor, treatment in CACON.

[f] p-value < 0.001. The following variables were candidates for the multiple models:

[g] black, asian, brown and indigenous

[h] p-value < 0.05

[i] married or civil union

[j] widowed, divorced or single

15.0% of the cases of this neoplasm were diagnosed at stage IV [14]. Such evidence, added to the fact that its screening is not recommended in Brazil and the approaches for its diagnosis are invasive, expensive or moderately accurate [21] reflect the demand for better approaches for early detection.

Regarding stage IV at diagnosis of cervix uteri cancer, even though it is a preventable disease due to early detection and the possibility of treating premalignant lesions [22], in addition to the recommendation for active screening in Brazil [20], there was an increase in APC from 2000-2019 (+4.8%, $p < 0.001$). Corroborating these data, Renna Junior and Silva [5] found that the diagnosis of this neoplasm at stages III and IV increased from 2000-2012 (APC: +1.1%; 95% CI: 0.8%−1.5%). Thuler et al. [10] demonstrated that the frequency of late diagnosis (≥IIB) increased from 32.8% between 2000 and 2004–35.5% between 2005 and 2009, reflecting failures in screening [23] and loss of diagnostic opportunities for symptomatic women in unresolved passages through primary and secondary health services [5].

Stage IV at diagnosis of colorectal cancer showed a high frequency and continuously increasing APC in both sexes (+1.2%, $p < 0.001$). Early detection of this neoplasm can occur through screening and early diagnosis [21]. However, early colorectal lesions are not usually symptomatic [24], which adds to the fact that Brazil does not have strategies for screening them in the public network [25], contributing to late diagnosis. The analyses of the ICESP hospital records, from 2008-2014 show that 36.7% of the cases between 18 and 39 years and 29.2% of those over 40 years of age were diagnosed in stage IV [13].

The delay in oncological diagnosis, particularly lung cancer, is one of main challenges faced in the country. In addition to the higher frequency of stage IV at diagnosis of lung cancer, there is an increasing APC (female 2000–2012: +2.7%, $p < 0.001$/ 2012–2019: +1.4%, $p = 0.030$; male 2000–2009: +1.6%, $p = 0.002$ and 2012–2019: +1.2%, $p = 0.023$). In Brazil, its screening is not recommended, and it is unlikely to be diagnosed early, as its symptoms usually occur in an advanced stage of the disease [21]. In most countries, this neoplasm is the main cause of cancer mortality, supported by its late diagnosis [26].

Regarding stage IV at diagnosis of female breast cancer, there was an initial retraction and subsequent increase in APC (2000–2003: −11.8%, $p = 0.003$ and 2013–2019: +3.3%, $p = 0.004$). A previous study, with data from the HCR, showed a retraction at stages III and IV from 2000-2002 (APC: −6.6%; 95% CI: −7.6% −5.5%) and an increase from 2002-2009 (APC: +1.1%; 95% CI: 0.9–1.3%) [6]. Despite the Brazilian guidelines recommending mammographic screening and early diagnosis [21], it is not uncommon for the diagnosis to occur late. Failed health systems [27], ineffective implementation of early detection programs and weaknesses in the monitoring of suspected cases corroborate this scenario [28].

Prostate cancer (APC 2000–2012: −5.4%, $p < 0.001$ and 2012–2017: +5.6%, $p < 0.001$) showed a similar trend to breast cancer. Despite the implementation of the National Policy for Full Attention to Men's Health in 2008 [29], this neoplasm is increasingly diagnosed late. Although it can be detected early through initial signs and symptoms [21], the search for preventive health care is not common among men [30]. From 1500 cases of prostate cancer diagnosed from 2000-2006 in Espírito Santo, a decrease was observed at stages III and IV [31]. In Minas Gerais, of the patients diagnosed between 2007 and 2012, 21.6% had stages III and IV [32].

The association of several variables with cancer diagnosed at stage IV was verified. According to the tumor site, age was associated with this outcome in different directions. Stage IV at diagnosis of colorectal, lung, stomach, lip and oral cavity, and thyroid cancer (OR ranging from 0.70 to 0.83, $p < 0.001$)], the inverse association with age > 60 years may reflect common practices among older individuals. The literature proves higher proportions of stages III and IV at diagnosis of colorectal, lung and stomach cancer in adults aged 18–39 years [13]. In all other tumor sites, there was a direct association between age > 60 years (OR ranging from 1.10 to 3.99, $p < 0.001$) and stage IV at diagnosis. In prostate

Table 3
Factors associated with the stomach, esophagus, colorectal, lip and oral cavity and thyroid cancer diagnosed in the stage IV in patients included in the integrated hospital-based cancer registry system in Brazil from 2000-2019.

Variables	Digestive tract						Lip and oral cavity		Thyroid	
	Upper				Lower					
	Stomach		Esophagus		Colorectal					
	Univariate	Multivariate[a]	Univariate	Multivariate[b]	Univariate	Multivariate[c]	Univariate	Multivariate[d]	Univariate	Multivariate[e]
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Age groups (years)										
<60	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>60	0.87 (0.84;0.90)[f]	0.83 (0.81;0.89)[f]	4.53 (4.39;5.12)[f]	3.99 (3.42;4.21)[f]	0.83 (0.80;0.85)[f]	0.82 (0.80;0.87)[f]	0.71 (0.66;0.75)[f]	0.70 (0.68;0.75)[f]	0.79 (0.76;0.83)[f]	0.81 (0.76;0.87)[f]
Sex										
Male	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.87 (0.84;0.90)[f]	0.86 (0.84;0.90)[f]	0.41 (0.38;0.44)[f]	0.42 (0.39;0.46)[f]	0.91 (0.89;0.96)[f]	0.91 (0.89;0.93)[f]	0.66 (0.64;0.69)[f]	0.72 (0.69;0.75)[f]	0.75 (0.72;0.80)[f]	0.80 (0.76;0.85)[f]
Race/ skin color										
White	1.00	–	1.00	–	1.00	–	1.00	1.00	1.00	–
Non-white[g]	0.97 (0.93;1.01)	–	0.72 (0.65;0.80)[f]	–	1.01 (1.01;1.04)[h]	–	1.30 (1.24;1.36)[f]	1.25 (1.17;1.41)[f]	1.07 (1.01;1.13)[f]	–
Missing data	1.00 (0.96;1.03)	–	0.59 (0.54;0.65)[f]	–	0.91 (0.89;0.93)[h]	–	1.14 (1.09;1.18)[h]	1.13 (0.94;1.33)	1.43 (1.36;1.51)[f]	–
Years of study										
<7	1.01 (0.97;1.04)	–	2.47 (2.27;2.70)[f]	1.81 (1.65;2.00)[f]	0.91 (0.89;0.94)[f]	0.93 (0.91;0.96)[f]	1.08 (1.04;1.12)[f]	1.10 (1.06;1.14)[f]	0.87 (0.83;0.97)[h]	–
>7	1.00	–	1.00	1.00	1.00	1.00	1.00	1.00	1.00	–
Missing data	1.02 (0.97;1.06)	–	1.19 (1.08;1.32)[f]	1.15 (1.04;1.28)[h]	0.91 (0.88;0.93)[f]	0.95 (0.92;0.97)[h]	1.13 (1.07;1.18)[f]	1.10 (1.04;1.26)[f]	0.87 (0.82;0.99)[h]	–
Marital status										
With partner[i]	1.00	–	1.00	–	1.00	1.00	1.00	1.00	1.00	1.00
Without partner[j]	1.01 (0.95;1.07)	–	0.76 (0.68;0.86)[f]	–	1.09 (1.04;1.13)[f]	1.06 (1.02;1.11)[h]	1.34 (1.27;1.40)[f]	1.21 (1.15;1.27)[f]	1.23 (1.15;1.31)[f]	1.18 (1.10;1.26)[f]
Missing data	0.98 (0.95;1.02)	–	0.68 (0.62;0.74)[f]	–	0.93 (0.91;1.07)	0.95 (0.89;1.03)	1.03 (0.99;1.06)	1.04 (0.93;1.16)	1.44 (1.37;1.50)[h]	1.03 (0.92;1.17)
Region of residence										
North, Northeast and Midwest	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	–
South and Southeast	1.03 (0.99;1.07)	1.08 (1.04;1.13)[h]	1.08 (0.99;1.16)	1.04 (1.02;1.10)[f]	1.03 (1.00;1.06)	1.09 (1.05;1.13)[h]	1.18 (1.04;1.12)[h]	1.13 (1.04;1.23)[f]	1.09 (1.03;1.16)[h]	–
Missing data	0.69 (0.54;1.01)	0.74 (0.64;1.21)	0.96 (0.49;1.89)	0.99 (0.99;2.58)	0.83 (0.69;1.01)	0.92 (0.76;1.11)	0.70 (0.53;1.13)	0.82 (0.61;1.10)	0.82 (0.56;1.20)	–
Current smoking										
No	1.00	–	1.00	1.00	1.00	–	1.00	1.00	1.00	–
Yes	1.04 (0.00;1.11)	–	2.17 (1.84;2.57)[f]	1.76 (1.47;2.10)[f]	0.95 (0.91;1.00)	–	1.47 (1.40;1.54)[f]	1.32 (1.26;1.39)[f]	0.99 (0.93;1.06)	–
Missing data	1.01 (0.97;1.04)	–	0.67 (0.61;0.73)[f]	0.83 (0.65;1.01)	0.92 (0.90;0.95)	–	1.15 (1.10;1.21)[f]	0.98 (0.92;1.05)	1.28 (0.99;1.35)	–
More than one primary tumor										
No	1.00	1.00	1.00	–	1.00	1.00	1.00	–	1.00	1.00
Yes	1.20 (1.06;1.36)[h]	1.19 (1.06;1.35)[h]	1.68 (1.27;2.22)[f]	–	1.37 (1.27;1.48)[f]	1.37 (1.26;1.49)[f]	0.55 (0.50;0.61)[h]	–	1.46 (1.24;1.69)[f]	1.45 (1.25;1.67)[f]
Missing data	0.98 (0.95;1.01)	0.94 (0.90;1.07)	0.72 (0.66;0.77[f]	–	0.92 (0.90;1.07)	0.85 (0.79;1.01)	0.92 (0.89;0.95)[h]	–	1.44 (1.38;1.51)[f]	1.36 (1.21;1.52)[f]
Referenced by SUS										
No	1.00	–	1.00	1.00	1.00	1.00	1.00	–	1.00	–
Yes	0.99 (0.94;1.05)	–	1.71 (1.53;1.91)[f]	1.32 (1.16;1.50)[f]	1.14 (1.09;1.19)[f]	1.12 (1.09;1.19)[f]	1.11 (1.04;1.18)[f]	–	0.99 (0.91;1.09)	–
Missing data	0.98 (0.93;1.04)	–	1.07 (0.96;1.19)	0.91 (0.83;1.05)	1.04 (0.99;1.08)	1.19 (1.13;1.28)[f]	1.01 (0.95;1.07)	–	1.39 (0.97;1.53)	–
Treatment in CACON										
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.09 (1.05;1.12)[f]	1.10 (1.07;1.14)[f]	0.85 (0.78;0.91)[f]	0.85 (0.78;0.93)[f]	1.08 (1.06;1.11)[f]	1.11 (1.08;1.16)[f]	1.06 (1.02;1.09)[h]	1.07 (1.05;1.12)[f]	1.33 (1.28;1.39)[f]	1.24 (1.19;1.30)[f]
Missing data	1.19 (0.88;1.62)	1.20 (0.89;1.65)	1.07 (0.96;1.19)	1.00 (0.40;2.61)	0.90 (0.69;1.17)	0.91 (0.71;1.21)	1.40 (0.94;2.10)	1.60 (0.99;1.70)	1.13 (0.70;1.80)	1.25 (0.78;2.01)

Note: OR= odds ratio; CI= confidence interval; SUS= Sistema Único de Saúde (National Health System); CACON= High Complexity Oncology Centers.
[a] age groups, sex, race/ skin color, region of residence, current smoking, more than one primary tumor and treatment in CACON;

[b] age groups, sex, race/ skin color, years of study, marital status, region of residence, current smoking, more than one primary tumor, referenced by SUS and treatment in CACON;
[c] age groups, race/skin color, years of study, marital status, geographic regions, current smoking, more than one primary tumor, referred by SUS, treatment in CACON;
[d] age groups, sex, race/ skin color, years of study, marital status, region of residence, current smoking, more than one primary tumor, referenced by SUS and treatment in CACON;
[e] age groups, sex, race/ skin color, years of study, marital status, region of residence, more than one primary tumor and treatment in CACON.
[f] p-value < 0.001. The following variables were candidates for the multiple models:
[g] black, asian, brown and indigenous
[h] p-value < 0.05
[i] married or civil union
[j] widow, divorced or single

cancer, for example, symptoms increase with advancing age due to progressive tumor growth [33]. Regarding cervix uteri cancer, a growing relationship between age groups and diagnosis in stages III and IV was previously demonstrated (45–49 years OR= 1.65; >70 years OR= 2.24)[5].

There was a direct association between female sex and stage IV at diagnosis in lung cancer (OR= 1.11, 95% CI: 1.08–1.14) and an inverse association in stage IV at diagnosis of colorectal, stomach, lip and oral cavity, esophagus, and thyroid cancer (OR varying from 0.42 to 0.91, p < 0.001). The incidence of lung cancer has increased in women, probably due to the increased prevalence of smoking among Brazilian women [34,35]. However, as it is not a traditionally recognized risk group, the diagnosis of the disease may have been delayed among females. Despite this, it was found that, in most neoplasms, the male gender was, in itself, a factor associated with stages III and IV at diagnosis [36], because, among other factors, this group tends to devalue their needs and seek health services mainly because of more advanced symptoms [31].

The inverse association of non-white skin color with stage IV at diagnosis of prostate (OR= 0.83, 95% CI: 0.80–0.85) and cervix uteri cancer (OR= 0.88, 95% CI: 0.84–0.94) was different than we expected, since skin color can be considered a marker of social status in Brazil, with non-white skin color related to worse socioeconomic status and, consequently, access to health services [37]. However, it is worth noting that, in addition to skin color having a high percentage of missing data (43.1%), cannot ignore the racial miscegenation present in Brazil. A study carried out in the United States showed that black and white people had similar chances of being diagnosed at stages III and IV prostate cancer [38].

On the other hand, the non-white skin color was directly associated with stage IV at diagnosis of cancer breast (OR= 1.09, 95% CI: 1.05–1.12) and lip and oral cavity (OR: 1.25, 95% CI: 1.17–1.41). Regarding the diagnosis of breast cancer in stages III and IV, studies reveal a higher proportion in black and brown women [4,6]. North American data showed that the odds of being diagnosed with stage III and IV oral cavity cancer were 2.1 (95% CI: 1.5–2.9) times higher in black than in white people [39].

Despite the different directions of associations, it was observed that lower education was directly associated with stage IV at diagnosis of breast, prostate, cervix uteri, lip and oral cavity, and esophagus cancer (OR ranging from 1.08 to 1.81, p < 0.001). Santos–Silva et al. [4] demonstrated that the diagnosis of breast cancer at stages III and IV was inversely associated with education (p < 0.001). Similarly, a study in India showed that the lower the level of education, the greater the chance of being diagnosed with stage III and IV cancer of the breast (p < 0.001), cervix uteri (p = 0.002) and lip and oral cavity (p < 0.001) [40].

Not living with a partner was directly associated with stage IV at diagnosis of breast, prostate, colorectal, lung, lip and oral cavity, thyroid and corpus uteri cancers (OR ranging from 1.06, p < 0.050–1.27, p < 0.001). Renna Junior & Silva [6] found that single women (OR: 1.46; 95% CI: 1.35–1.56) were more likely to be diagnosed at stages III and IV of breast cancer. In a study of the North American population, divorced, single and widowed patients with prostate cancer were 1.1 times more likely to have stage III disease than those who were married [41]. According to cases diagnosed between 1992 and 2008 in Denmark, frequencies of stages III and IV increased in men living alone [42]. Not living with a partner may mean having less support for seeking health care and diagnosis, as well as adopting a less restrained lifestyle [41].

Smoking was directly associated with stage IV at diagnosis of breast, prostate, lung, lip and oral cavity and esophagus cancers (OR ranging from 1.05, p < 0.050–1.76, p < 0.001). Smoking is known to be a factor of high carcinogenic potential, especially for cancer of the hypopharynx, lung, larynx, oropharynx and oral cavity and esophagus [43,44]. However, evidence regarding this association with stage IV at diagnosis is scarce. A US study found an increased risk of incurable prostate cancer among smokers [45].

Having more than one primary tumor was directly associated with stage IV at diagnosis of breast, prostate, cervix uteri, colorectal, stomach and thyroid cancers (OR ranging from 1.19, p < 0.050–1.54, p < 0.001). Although the specialized literature is very limited in terms of evidence in this regard, it is known that the difficulty in diagnosing an additional primary tumor in patients with a previous history of cancer, in which metastases may develop from the first tumor site, may corroborate the late diagnosis [46].

In relation to Brazilian geographic regions, we found that living in the South and Southeast was inversely associated with stage IV at diagnosis of prostate (OR= 0.93, 95% CI: 0.91–0.96) and lung (OR= 0.93, 95% CI: 0.91–0.96) and directly associated in breast cancer, cervix uteri, colorectal, stomach, lip and oral cavity, and esophagus (OR ranging from 1.04 to 1.13, p < 0.001). Scientific literature is scarce and divergent in relation to late cancer diagnosis in different regions of the country. Renna Junior & Silva [5] found that women from all regions, compared to those in the Southeast, were more likely to be diagnosed with cervix uteri cancer in stages III and IV (OR ranging from 1.15 to 2.55). As for breast cancer, women living in the North, Northeast and Midwest regions were more associated with stage ≥IIB (OR=1.27, 95% CI: 1.21–1.33) [47].

In this study, SUS referral for cancer treatment was directly associated with stage IV at diagnosis of breast, colorectal, esophageal, and corpus uteri cancer (OR ranging from 1.12 to 1.32, p < 0.001). Currently, about 70.0% of the Brazilian population depends on public health services of SUS [48] and has difficulties in accessing cancer diagnosis and treatment, with delays in scheduling appointments, diagnostic investigation and referral to cancer centers [49], which is associated with a higher probability of having cancer diagnosed in advanced stage [8].

Additionally, it was found that being treated with CACON was inversely associated with stage IV at diagnosis of prostate cancer (OR= 0.91; 95% CI: 0.89–0.93) and esophagus (OR= 0.85; 95% CI: 0.78–0.93) and directly associated with breast, colorectal, stomach, lip and oral cavity, and thyroid cancers (OR ranging from 1.03, p < 0.050–1.24, p < 0.001). In CACONs, where treatments of high complexity and technological density are offered to control cancer [50], there was a higher frequency of advanced cancer. This evidence reflects the need for the reorganization of health policies and services to make faster

diagnosis of symptomatic cases and to provide comprehensive and integrated care, proportional to the stage of the disease, for patients with advanced cancer.

Therefore, it is possible to affirm that having social vulnerability was directly associated with cancer diagnosed at stage IV. Identifying the factors associated with this outcome makes it possible to direct public health policies, priority programs and strategic investments in the country. It is necessary to guarantee access to the diagnosis of symptomatic cases, especially among those at risk. Efforts should be focused on modifiable factors, such as promoting quality education, health awareness and make health services available in the country, considering the most vulnerable geographic areas and social profiles. In clinical practice, it is important that health professionals are aware of high-risk symptomatic cases. Efforts to accelerate cancer diagnosis can promote improved survival and quality of life [51].

However, some limitations must be mentioned. The incompleteness of information recorded in the databases, whether due to the quality of information available on each diagnosed case or to the individual responsible for recording it in the database [52], is a factor that must be considered. In our analysis, we found that for most types of cancer evaluated, the degree of incompleteness of information regarding clinical staging was considered poor. Knowing that there is a greater possibility of under-registration in poorer regions [53], it is likely that the records of cancer diagnosed at stage IV were mainly affected, whose frequency may be higher than we described. The high percentage of data missing from independent variables such as skin color, smoking, referral by the SUS, marital status and having more than one primary tumor should also be considered important limitations.

Furthermore, it is difficult to estimate how complete the investigation of the cases is. Thus, as the data were obtained from a secondary basis, they could not be analyzed directly and, for example, it is not possible to check whether the data related to stage IV of corpus uteri cancer are correct. As the RHC includes cases treated in cancer centers and mainly covers SUS users, its data do not represent the entire Brazilian population. Despite the growing coverage in recent years, it is worth noting that there are more RHCs in the Southeast regions of the country.

In addition, although one of the objectives of this study was the analysis of temporal trends in the cancer diagnosed at stage IV, not all RHCs have data for the period of 20 years due to recent implementation [54]. The lack of publications at stage IV diagnosis based on information from RHCs makes it difficult to compare results. Despite these limitations, most of the findings of this investigation are consistent with the scarce evidence described in the literature.

It is worth noting that the data from the present study refer to the period before the COVID-19 pandemic, from which numerous services such as cancer screening and diagnosis [55] were interrupted, reflecting the perspective that, from now until the following years, an even higher frequency of cancer diagnosed at stage IV than we have seen [56]. However, as a strong point, it is highlighted that the results of this study represent public oncology care in the country, since the HCR increasingly cover most of the oncology health units accredited by the SUS.

5. Conclusion

We conclude that there is a high frequency and increasing trend of cancer diagnosed at stage IV, whose risk of occurrence can be affected by different sociodemographic, lifestyle and clinical factors. Thus, this study can help to understand issues related to public cancer care in Brazil, supporting the planning of policies and strategies to reduce stage IV at diagnosis.

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CRediT authorship contribution statement

Livia Costa de Oliveira: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Investigation. **Karla Santos da Costa Rosa:** Methodology, Visualization, Investigation, Writing – review & editing. **Anke Bergmann:** Conceptualization, Methodology, Data curation, Supervision, Resources, Writing – review & editing. **Luiz Claudio Santos Thuler:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Supervision, Writing – review & editing.

Declarations of interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2022.102242.

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