Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

The Quality of Pap Smears from the Brazilian Cervical Cancer Screening Program According to the Human Development Index

Ricardo Filipe Alves Costa[1,2], Adhemar Longatto-Filho[3,4,5,6], Fabiana de Lima Vazquez[7], Céline Pinheiro[2,3], Luiz Carlos Zeferino[8], and José Humberto Tavares Guerreiro Fregnani[7,9]

ABSTRACT

Brazil is a country with strong socioeconomic disparities, which may explain the different rates of cervical cancer incidence and mortality and influence the quality of cervical cancer screening tests. The aim of this study was to perform a trend analysis of some quality indicators of Pap smears according to the Municipal Human Development Index (MHDI). Information about cytopathological exams (approximately 65,000,000) performed from 2006 to 2014 in women ages 25 to 64 years was obtained from the Cervical Cancer Information System (SISCOLO). The average annual percentage change (AAPC) for each indicator was calculated using the Joinpoint Regression Program, according to MHDI levels. Very low frequencies of unsatisfactory cases (<5%) were observed at different MHDI levels. Although the positivity index in the low- and medium-MHDI groups has increased, the values remained below international recommendations (3%–10%). The HSIL (high-grade squamous intraepithelial lesion) percentage remained stationary at all levels of the MHDI. In the low- and medium-MHDI groups, most quality indicators were below the recommendations by Brazilian National Cancer Institute INCA, with no improvement trend; in the high-MHDI group, the majority of the indicators also presented no improvement, although they show slightly better quality indicators. The MHDI should be considered in the definition of the policies of the screening program for cervical cancer in Brazil, and the current program may require adjustments to achieve improved efficiency.

Introduction

Cervical cancer, with an estimated 570,000 new cases and 311,000 deaths in 2018 worldwide, is the fourth-most frequently diagnosed cancer and the fourth-leading cause of cancer-related death in women. In regions with lower Human Development Index (HDI), an indicator that includes education, life expectancy and per-capita income that is widely used to classify countries according to their level of development and socioeconomic profile, cervical cancer is the second-most common in incidence and mortality (1).

Brazil is divided into five macroregions, 26 states and one federal district, and 5,570 municipalities (5,565 before the year 2013) and shows distinct socioeconomic realities, with regions comparable with high-income to low-income countries. In 2017, Brazil was classified as a high HDI country (0.759; http://hdr.undp.org/en/countries/profiles/BRA), whereas in 2010, the Municipal Human Development Index (MHDI) varied from 0.418 (Melgaço) to 0.862 (São Caetano; http://www.atlasbrasil.org.br/2013/pt/download). Possibly because of these MHDI disparities, the incidence and mortality rates of cervical cancer vary widely in Brazil. For 2019, 16,379 new cases are estimated in Brazil, with an estimated risk of 15.43/100,000 women, as cervical cancer is the third-most common cancer among women.

Brazil has a single cervical cancer opportunistic screening program based on the Pap test (screening is non-population based), which is recommended for women between 25 and 64 years of age who have initiated sexual activity. The test is recommended every 3 years after two normal tests in a period of one year (2).

Previous studies by our group have shown that most of the quality indicators of cytological tests in Brazil are still below the values recommended by the Brazilian National Cancer Institute (INCA) and the Ministry of Health (3) and that there is a discrepancy in value indicators and their trend by region and state, possibly due to socioeconomic factors (4). Therefore, the

[1]Graduate Program on Oncology, Barretos Cancer Hospital, Barretos, São Paulo, Brazil. [2]Barretos School of Health Sciences Dr. Paulo Prata—FACISB, Barretos, São Paulo, Brazil. [3]Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, São Paulo, Brazil. [4]Laboratory of Medical Investigation (LIM 14), Faculty of Medicine, São Paulo University, FMUSP, São Paulo, Brazil. [5]Life and Health Sciences Research Institute, ICVS, School of Health Sciences, Minho University, Braga, Portugal. [6]ICVS/3B's—PT Government Associate Laboratory, Braga/Guimarães, Portugal. [7]Research and Teaching Institute, Barretos Cancer Hospital, Barretos, São Paulo, Brazil. [8]School of Medical Sciences, Women's Hospital CAISM, Unicamp, Campinas, São Paulo, Brazil. [9]A.C. Carmargo Cancer Center, São Paulo, Brazil.

Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Corresponding Author: Ricardo Filipe Alves da Costa, Barretos School of Health Sciences, Dr. Paulo Prata—FACISB, Avenida Loja Maçonica Renovadora 68, N 100, Barretos 14785-002, Brazil. Phone: 55-17-3321-3060; Fax: 55-17-3321-3068; E-mail: ricardofacosta@gmail.com

Cancer Prev Res 2020;13:299–308

doi: 10.1158/1940-6207.CAPR-19-0306

©2019 American Association for Cancer Research.

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

aim of this study was to evaluate the quality of cytological tests performed at different HDI levels.

Materials and Methods

This is a time–series analysis of the quality of Pap smears in Brazil for women ages 25 to 64 years old, evaluated according to MHDI. This index adjusts the HDI to the municipal reality and reflects specific and regional challenges in Brazilian human development (5). The MHDI is measured on a scale ranging from 0 to 1; the closer the value is to 1, the greater the human development. The MHDI values are divided into five categories: very high ($\geq$0.800), high (0.700–0.799), medium (0.600–0.699), low (0.500–0.599), and very low (<0.500; ref. 5). We grouped the MHDI into 3 categories as follows: high (MHDI$\geq$0.700), medium (0.600$\leq$MHDI<0.700), and low (MHDI<0.600). The distribution of municipalities according to HDI is shown in Supplementary Fig. S1.

Data related to the Pap smears were collected from the publicly available Information System of Cervical Cancer Screening (SISCOLO, http://www2.datasus.gov.br/DATASUS/index.php), created in 1999 by the INCA and the Department of Informatics of the public health system to manage and monitor the Brazilian cervical cancer screening program. In brief, SISCOLO contains information on all Pap tests performed in the public system, including first-level screening tests as well as follow-up Pap tests, providing the number of exams performed (not the number of women who submitted to the exams). The cytology results are classified according to a standard adapted from the Bethesda System, and the main screening method is the Pap smear; however, liquid cytology is being incorporated in some primary health units (6). The data were collected by municipality (information on 5,565 municipalities) from cytopathological exams performed on women ages 25 to 64 years who voluntarily participated in the opportunistic Brazilian governmental program of cervical cancer prevention from January 2006 to December 2014, according to collection unit (preanalytical indicators) or service provider (analytical indicators).

The following information was not available in SISCOLO: The results of ASC-H (atypical squamous cells of undetermined significance—high grade), HSIL with possible microinvasion and transformation zone from January to June 2006, as well as data from the state of Amapá from January 2013 to the closing of this study. In addition, inconsistent data (excessive number of exams) were observed in the state of Acre in 2006; consequently, these data were not included in the analysis.

The number of women ages 25 to 64 years and living in municipalities in the years from 2006 to 2013 was obtained from the Department of Informatics of the public health system (http://tabnet2.datasus.gov.br/cgi/deftohtm.exe?idb2013/a01.def) to determine the productivity rate. The number of women from 2014 was not collected because information regarding the number of exams was lacking from the last months of 2014; this limitation did not influence the determination of the other indicators.

The following quality indicators were determined for women ages 25 to 64 years: (i) productivity rate (the ratio between the number of exams performed and the number of women ages 25–64 years); (ii) the percentage of unsatisfactory exams; (iii) the percentage of cases with representations of the transformation zone (region of the cervix where the columnar epithelium has been and/or is being replaced by new metaplastic squamous epithelium); (iv) positivity index (prevalence of cell alterations in satisfactory exams); (v) ASC-US percentage; (vi) ASC-H percentage; (vii) ASC (atypical squamous cells) percentage; (viii) LSIL percentage; (ix) HSIL percentage (including HSIL with possible microinvasion); (x) ASC/abnormal percentage; and (xi) ASC/SIL ratio. The formulas used to obtain the indicators are shown in **Table 1**.

Table 1. Formulas for calculating quality indicators and respective reference values.

	Indicators	Calculation	Reference values
Preanalytical	Productivity rate (%)	$\frac{\text{number of exams performed}}{\text{number of women}} \times 100$	Not applicable
	Unsatisfactory (%)	$\frac{\text{number of unsatisfactory exams}}{\text{number of exams performed}} \times 100$	1%[a] (Average of the collected exams in Brazil in 2010)
	Transformation zone (%)	$\frac{\text{number of transformation zone exams}}{\text{number of satisfactory exams}} \times 100$	Not applicable
Analytical	Positivity Index (%)	$\frac{\text{number of abnormal exams}}{\text{number of satisfactory exams}} \times 100$	3%–10%[a]
	ASC-US (%)	$\frac{\text{number of ASC–US exams}}{\text{number of satisfactory exams}} \times 100$	Not applicable
	ASC-H (%)	$\frac{\text{number of ASC–H exams}}{\text{number of satisfactory exams}} \times 100$	Not applicable
	ASC (%)	$\frac{\text{number of ASC exams}}{\text{number of satisfactory exams}} \times 100$	<4%–5%[a]
	LSIL (%)	$\frac{\text{number of LSIL exams}}{\text{number of satisfactory exams}} \times 100$	Not applicable
	HSIL (%)	$\frac{\text{number of HSIL exams}}{\text{number of satisfactory exams}} \times 100$	0.5%–1.0% (USA, 0.5%; Canada, 0.6%; UK, 1.1%; Norway, 1.1%)
	ASC/Abnormal (%)	$\frac{\text{number of ASC exams}}{\text{number of abnormal exams}} \times 100$	<60%[a]
	ASC/SIL	$\frac{\text{number of ASC exams}}{\text{number of SIL exams}}$	<3[a]

Note: Information on cytopathologic exams was obtained from women ages 25 to 64 years old.
Abbreviations: ASC, atypical squamous cells; ASC-H, atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SIL, squamous intraepithelial lesion.
[a]Reference values by Brazilian National Institute of Cancer (INCA).

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

This study was approved by the Ethics Committee of the Barretos Cancer Hospital.

Data processing and statistical analysis

R software (The R Foundations for Statistical Computing) and Microsoft Excel 2013 (Microsoft Corporation 2013) were used to organize the collected data, create new spreadsheets, and calculate the quality indicators according to the MHDI.

Joinpoint Regression Program Version 4.5.0.1 (June 2017; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) was used to calculate, for each indicator, the annual percentage change (APC) for each trend identified, using the minimum number of joinpoints/inflection points (a maximum of 1 joinpoint was tested; in case of one inflection point, trend 1 and trend 2 were calculated, whereas only one trend (trend 1) was calculated in case of zero joinpoints), and the average annual percentage change (AAPC), which is a summary measure over a fixed interval. Each significant point indicates an increase or decrease in the rate (7). To describe linear trends, the APC and AAPC values and the respective 95% confidence intervals (95% CI) were computed. When the best model fit has zero joinpoints, the APC and AAPC are identical.

Results

A total of 65,882,438 exams in the target age range (25–64 years) were performed in Brazil from 2006 to 2014. Supplementary Table S1 shows the distribution of exams according to cytological results and categories of MHDI, considering the municipality of the collection unit (preanalytical indicators) or service provider (analytical indicators). **Figure 1** shows the distribution of exams per age range, where a significant decrease in the percentage of exams performed in women ages 25 to 34 years and a significant increase in the percentage of exams performed in women ages 35 to 54 years were observed. Supplementary Table S2 shows the values for each indicator, and **Table 2** shows the corresponding APC and AAPC values. **Figures 2** and **3** show the trend lines.

In the high-MHDI group, the trends of the productivity rate, the percentage of unsatisfactory exams, the percentage of the transformation zone, the positivity index and percentage of HSIL remained stationary. A yearly significant increase was observed in the percentage of ASC-US (AAPC = 3.51), percentage of ASC-H (AAPC = 4.78), percentage of ASC (AAPC = 3.90), percentage of ASC/abnormal (AAPC = 2.81) and ASC/SIL ratio (AAPC = 6.94), and a significant decrease was observed in the percentage of LSILs (AAPC = −3.64). It should be noted that a different behavior in the trend during the period under study was observed for the percentage of ASC-H, which remained stationary until 2009 and underwent a significant increase of 7.57% per year from 2009 to 2014, and for the percentage of LSIL, which suffered a significant decrease of 7.84% per year from 2006 to 2009 and then remained stationary until 2014.

In the medium-MHDI group, during the period under study, the trend of the percentage of HSIL remained stationary over time. There was a significant increase in the positivity index (AAPC = 1.40), percentage of ASC-US (AAPC = 6.92), percentage of ASC-H (AAPC = 6.28), percentage of ASC (AAPC = 11.17), percentage of ASC/abnormal (AAPC = 4.92) and ASC/SIL ratio (AAPC = 9.33). A yearly significant decrease was observed in the productivity rate (AAPC = −2.62), percentage of unsatisfactory exams (AAPC = −3.39), percentage of transformation zone (AAPC = −2.27), and percentage of LSIL (−2.14). Note the different behavior in the trend during the period under study for the positivity index, which remained stationary until 2008 and underwent a significant increase of 1.40% per year from

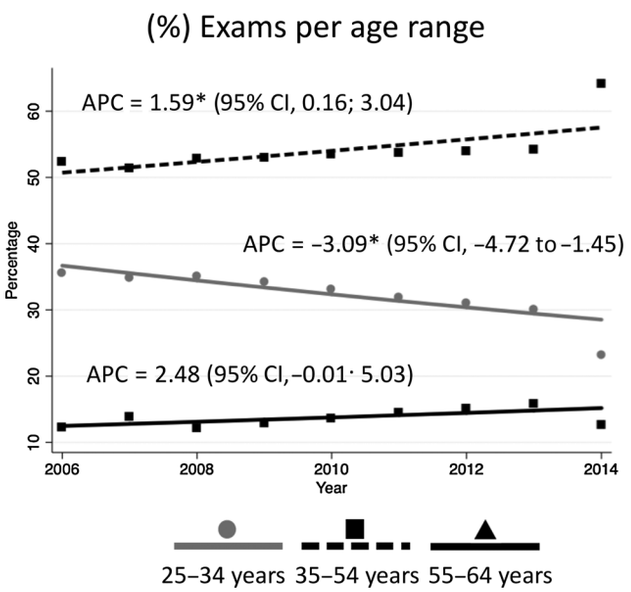

Figure 1.

Time series of the percentage of exams per age range from 2006 to 2014. * APC is significantly different from zero (P <0.05).

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

Table 2. Quality indicator trends by Brazilian Municipal Human Development Index from 2006 to 2014.

Indicator	MHDI	Trend 1				Trend 2				AAPC		
		Period	APC	95% CI		Period	APC	95% CI			95% CI	
				LL	UL			LL	UL		LL	UL
Productivity Rate (%)	**High**	2006–2013	−1.95	−4.46	0.62	–	–	–	–	−1.95	−4.46	0.62
	Medium	2006–2013	−2.62[a]	−4.86	−0.33	–	–	–	–	−2.62[a]	−4.86	−0.33
	Low	2006–2013	−2.51[a]	−4.72	−0.24	–	–	–	–	−2.51[a]	−4.72	−0.24
Unsatisfactory exams (%)	**High**	2006–2011	−4.48	−9.50	0.82	2011–2014	11.06	−3.85	28.29	1.08	−3.37	5.73
	Medium	2006–2014	−3.39[a]	−4.67	−2.08	–	–	–	–	−3.39[a]	−4.67	−2.08
	Low	2006–2014	−3.68[a]	−6.56	−0.70	–	–	–	–	−3.68[a]	−6.56	−0.70
Transformation Zone (%)	**High**	2006–2014	−0.35	−1.07	0.38	–	–	–	–	−0.35	−1.07	0.38
	Medium	2006–2014	−2.27[a]	−3.01	−1.53	–	–	–	–	−2.27[a]	−3.01	−1.53
	Low	2006–2014	−2.45[a]	−3.19	−1.70	–	–	–	–	−2.45[a]	−3.19	−1.70
Positivity Index (%)	**High**	2006–2012	−0.30	−2.58	2.04	2012–2014	9.56	−7.90	30.33	2.08	−1.23	5.51
	Medium	2006–2008	−1.72	−8.27	5.29	2008–2014	2.47[a]	1.21	3.73	1.40[a]	0.01	2.81
	Low	2006–2014	4.39[a]	1.97	6.87	–	–	–	–	4.39[a]	1.97	6.87
% ASC–US	**High**	2006–2014	3.51[a]	1.23	5.84	–	–	–	–	3.51[a]	1.23	5.84
	Medium	2006–2014	6.92[a]	4.98	8.88	–	–	–	–	6.92[a]	4.98	8.88
	Low	2006–2014	6.51[a]	1.82	11.43	–	–	–	–	6.51[a]	1.82	11.43
% ASC–H	**High**	2006–2009	0.29	−6.98	8.13	2009–2014	7.57[a]	4.35	10.89	4.78[a]	2.30	7.33
	Medium	2006–2014	6.28[a]	4.08	8.53	–	–	–	–	6.28[a]	4.08	8.53
	Low	2006–2014	10.19[a]	4.33	16.38	–	–	–	–	10.19[a]	4.33	16.38
% ASC	**High**	2006–2014	3.90[a]	1.63	6.21	–	–	–	–	3.90[a]	1.63	6.21
	Medium	2006–2008	25.72[a]	11.10	42.27	2008–2014	6.70[a]	4.92	8.51	11.17[a]	8.58	13.82
	Low	2006–2014	6.94[a]	3.00	11.03	–	–	–	–	6.94[a]	3.00	11.03
% LSIL	**High**	2006–2009	−7.84[a]	−12.29	−3.17	2009–2014	−1.02	−3.78	1.81	−3.64[a]	−5.36	−1.88
	Medium	2006–2014	−2.14[a]	−4.01	−0.23	–	–	–	–	−2.14[a]	−4.01	−0.23
	Low	2006–2014	1.29	−2.36	5.07	–	–	–	–	1.29	−2.37	5.07
% HSIL	**High**	2006–2008	−7.70	−16.00	1.42	2008–2014	0.86	−0.77	2.50	−1.36	−3.18	0.51
	Medium	2006–2014	−1.18	−2.51	0.17	–	–	–	–	−1.18	−2.51	0.17
	Low	2006–2014	1.35	−3.00	5.90	–	–	–	–	1.35	−3.00	5.90
ASC/Abnormal (%)	**High**	2006–2014	2.81[a]	1.95	3.67	–	–	–	–	2.81[a]	1.95	3.67
	Medium	2006–2014	4.92[a]	3.84	6.01	–	–	–	–	4.92[a]	3.84	6.01
	Low	2006–2014	2.74	−0.73	6.33	–	–	–	–	2.74	−0.73	6.33
ASC/SIL	**High**	2006–2014	6.94[a]	4.95	8.96	–	–	–	–	6.94[a]	4.95	8.96
	Medium	2006–2012	7.68[a]	5.76	9.63	2012–2014	14.42[a]	2.87	27.28	9.33[a]	7.05	11.65
	Low	2006–2014	7.05[a]	3.13	11.13	–	–	–	–	7.05[a]	3.13	11.13

Abbreviations: AAPC, average annual percentage change; APC, annual percentage change; ASC, atypical squamous cells; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LL, lower limit; LSIL, low-grade squamous intraepithelial lesion; MHDI, Municipal Human Development Index; SIL, squamous intraepithelial lesion; UL, upper limit.

[a]APC is significantly different from zero ($P < 0.05$).

2008 to 2014, as well as for the ASC/SIL ratio, which underwent a significant increase of 7.68% per year from 2006 to 2012 and another significant increase of 9.33% per year from 2012 to 2014.

In the low-MHDI group, the trends of the percentage of LSIL, percentage of HSIL, and percentage of ASC/abnormal remained stationary over time. There was a significant increase in the positivity index (AAPC = 4.39), percentage of ASC-US (AAPC = 6.51), percentage of ASC-H (AAPC = 10.19), percentage of ASC (AAPC = 6.94) and ASC/SIL ratio (AAPC = 7.05). A significant decrease was observed in the productivity rate (AAPC = −2.51), percentage of unsatisfactory exams (AAPC = −3.68), and percentage of transformation zone (AAPC = −2.45).

Discussion

The Brazilian guidelines for cervical cancer screening recommend that women between 25 and 64 years old undergo a Pap test every 3 years if the results are normal, but many women with a normal Pap test undergo screening more than once every 3 years (8), with approximately 50% of Pap tests performed on an annual basis (9). In addition, part of the Brazilian population (approximately 25%) has private health insurance; these individuals seem to prefer using the private rather than the public system for Pap tests, and data from these exams are not included in SISCOLO. Compared with developing regions of Brazil, the developed regions of the country have a higher rate of individuals using the private health system (http://www.ans.

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

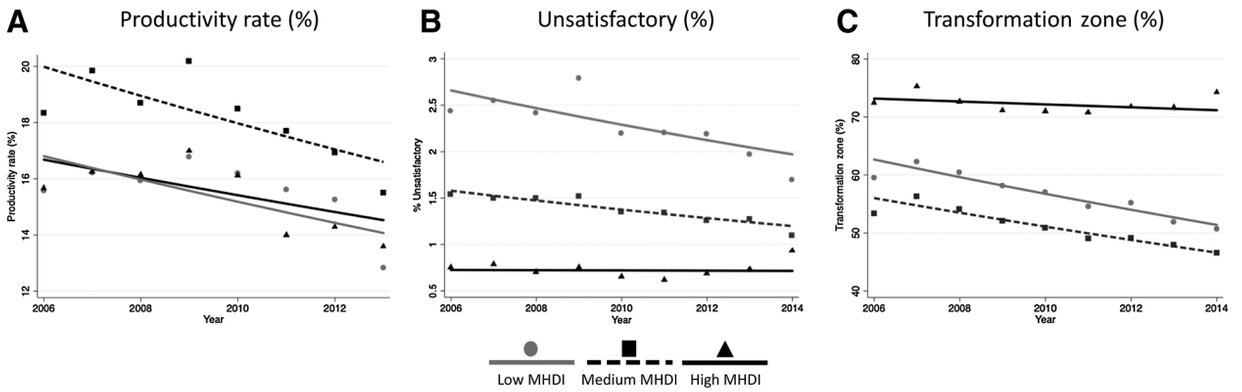

Figure 2.

Time series of the preanalytical quality indicators according to different levels of the Municipal Human Development Index from 2006 to 2014. (**A**) productivity rate (%); (**B**) % unsatisfactory exams; and (**C**) transformation zone (%). Models fit with zero joinpoints.

gov.br/anstabnet/cgi-bin/tabnet?dados/tabnet_tx.def), which may explain the similar productivity rates between regions with high and low MHDI.

The analysis of the preanalytical Pap test results showed that the percentages of unsatisfactory exams are within the range recommended by the WHO (<5%); however, only the group of municipalities with high MHDI follow the INCA recommendations (<1%). The numbers of unsatisfactory exams were higher in the low-MHDI groups, but the tendency of the number of unsatisfactory samples in this group of municipalities, as in the medium-MHDI group, has been decreasing. A previous study in Brazil showed similar results, with 0.4% of unsatisfactory exams in the state of Maceió and 0.2% in Rio de Janeiro (10). In addition, in 2002, a study involving 1,088 laboratories and 10,505,773 cytopathological exams from SISCOLO showed a percentage of unsatisfactory exams of 1.66%, with 25% of the laboratories having more than 2.0% of unsatisfactory samples (11). In 2010, of the 10,275,476 tests performed in public health, approximately 1.0% were considered unsatisfactory (12). In previous studies from our group using SISCOLO data, the average percentage of unsatisfactory samples in Brazil from 2006 to 2013 in women ages 25 to 64 years was approximately 1.0% (3), varying by region (from 0.41% in the South Region, a developed region, to 1.89% in the Northeast Region, an underdeveloped region) and state (from 0.27% in Paraná to 3.75% in Pernambuco; ref. 4).

The majority of cervical lesions begin to develop in the transformation zone (TZ), and the presence of epithelial cells from this region in the Pap test increases the likelihood of lesion identification (13, 14). We observed an expressive difference of approximately 15 percentage points in the indicator TZ%, with higher TZ% values in the high-MHDI group than in both the low- and medium-MHDI groups. In addition, the TZ% in the low- and medium-MHDI groups decreased in the period under study, possibly due to problems related to sample collection. In a study conducted in the state of Maranhão that used data collected from SISCOLO between 2007 and 2012, higher TZ percentages were found in municipalities with very low-MHDI (80.0%) when compared with medium/low- (59.1%) or high- (42.2%) MHDI municipalities (15); these results are contrary to those observed in our study. The authors explain the high TZ values in the very low-MHDI municipalities of Maranhão as a result of better technical preparation by the professionals performing the smear collection (15).

The preanalytical indicators of the Pap test are related to the quality of the sample collection performed in primary care units; therefore, the difference between MHDI groups in these indicators could result from developed areas being more attractive for well-trained and experienced technicians/physicians.

Regarding the analytical indicators, the positivity index is higher in the group of municipalities with high MHDI, although in the period under study, it showed a stationary tendency. In the low- and medium-MHDI groups, an increase in the positivity index was observed, but independently of the MHDI levels, the values observed are below those recommended by the INCA (3%–10%), suggesting that the quality of cytologic examination is low at all levels, especially for the low- and medium-MHDI groups. In a previous study, our group observed that the positivity index varied between 0.38 (Amapá) and 10.53 (Roraima) in Brazilian states and regions (4). Other studies have indicated that the states of Maranhão (15) and Maceió (10) show results below the recommended values (2.2% and 1.1%, respectively), whereas Rio de Janeiro (10) and Goiás (16) are within the recommended range (6.8% and 6.1%, respectively). Importantly, another study showed that Brazil has 627 (53%) cytopathology service providers with a positivity index below 2.0% (12), which is in accordance with the results obtained in the present study.

In countries that have a well-structured cytological screening program, such as the United States, England, and Norway, the reported positivity indexes are 4.3% (17), 5.9% (https://digital.nhs.uk/catalogue/PUB18932), and 5.7% (https://www.kreftregisteret.no/en/Cancer-prevention/Cervical-Cancer-Scfreening-Programme/Helsepersonell/Anual/), respectively. In the

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

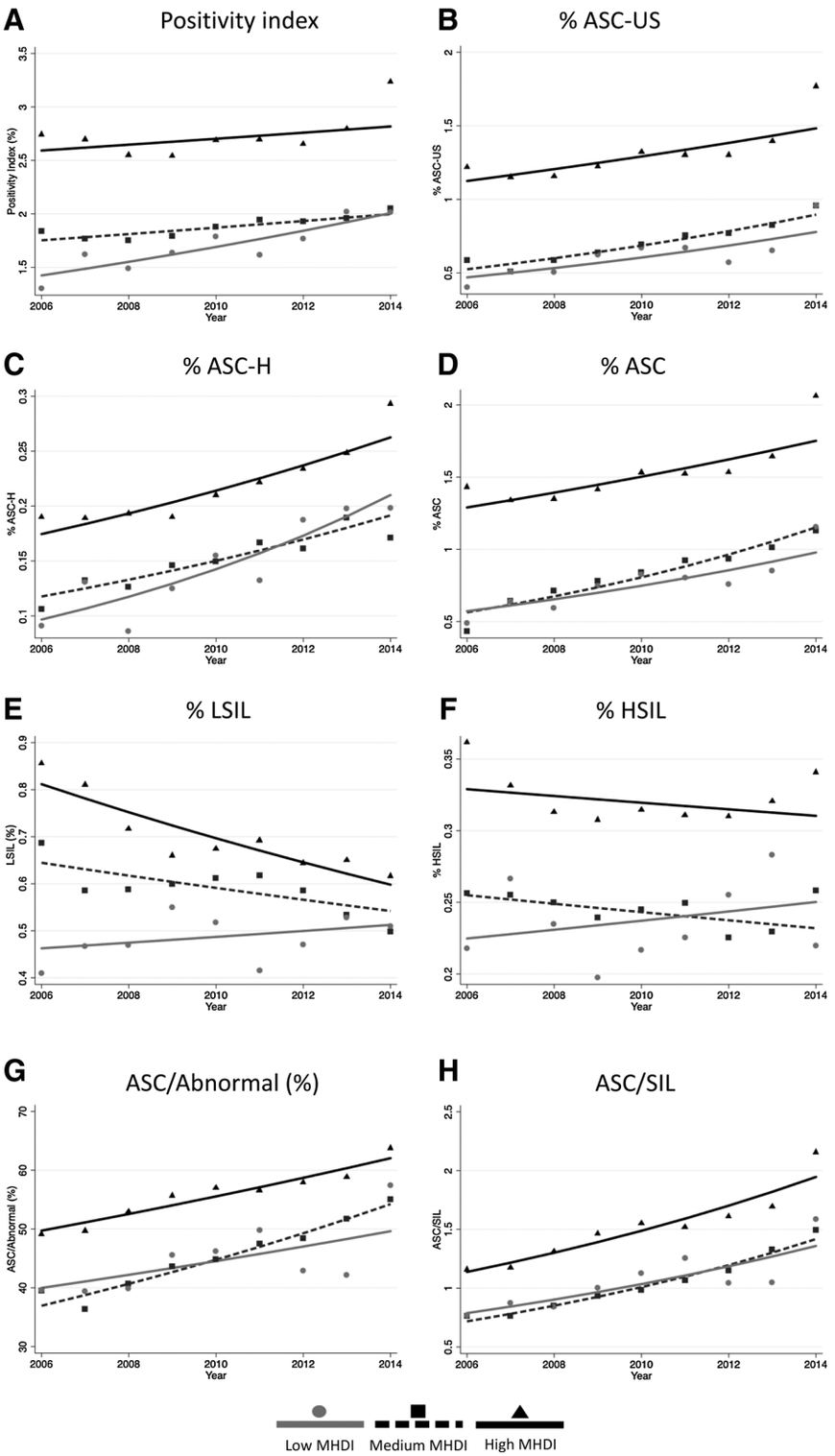

Figure 3.

Time series of the analytical quality indicators according to different levels of the Municipal Human Development Index from 2006 to 2014. **A,** positivity index (%); (**B**) ASC-US; (**C**) ASC-H (%); (**D**) ASC (%); (**E**) LSIL (%); (**F**) HSIL (%); (**G**) ASC/abnormal (%); and (**H**) ASC/SIL. ASC, atypical squamous cells; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; and SIL, squamous intraepithelial lesion. Models fit with zero joinpoints.

Athena trial, a 2009 study across the United States (61 centers in 23 states) in which 46,887 women ≥21 years old underwent liquid-based cytology, the abnormal exam rates ranged from 3.8% to 9.9% (18).

The detection of HSIL was, in the 3 groups of MHDI, below the range recommended by the INCA (0.5%–1.0%), with slightly better results observed in the high-MHDI group and very similar results in the medium- and low-MHDI groups. For

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

all groups, the trends were stationary. These results are in line with other studies describing a detection of HSIL or HSIL$^+$ of approximately 0.3% (3, 11, 15) but varying among states (0.1% in Maceió and 0.9% in Rio de Janeiro) and regions (0.21% in the Southeast Region and 0.49 in the North Region; refs. 4, 10). In developed countries such as the United States, England, and Norway, the detection of HSIL is 0.5% (17), 1.0% (https://digital.nhs.uk/catalogue/PUB18932) and 0.8% (https://www.kreftregisteret.no/screening/Om-forebyggende-undersokelser/), respectively. HSIL detection could be influenced by local factors, such as cervical cancer prevalence and incidence, and, as underdeveloped regions in Brazil have higher cervical cancer incidence compared with developed regions (19), a higher HSIL rate was expected in medium- and low-MHDI groups. The low ability to detect intraepithelial lesions observed in the present study can be a result of suboptimal slide preparation, high workload routine, limited continued education or even inadequate training of the professionals.

In all levels of the MHDI, an increase in the ASC/SIL ratio was observed as a result of increased detection of atypical squamous cells (ASC-US and ASC-H) and decreased detection of LSIL. This is typical of a cervical cancer screening performed in a population of older women who have a lower prevalence of LSIL and a higher prevalence of ASC, and as **Fig. 1** shows, there was a decrease in the number of exams performed on women ages 25 to 34 years and an increase in women ages 35 to 54 years.

Analytical indicators are associated with the quality of the laboratories and the professionals that analyze the Pap smears. To maintain an adequate level of competence, the Pan American Health Organization (PAHO) suggests that a laboratory process at least 15,000 exams annually (20). A Brazilian study from 2002 showed that among 739 participating laboratories, only 18.9% had performed at least 15,000 exams per year (11), suggesting that the majority of laboratories may be working with professionals who have not adequately developed their skills. The laboratories with high Pap test demands are in the most developed regions, regions that are most attractive to the most experienced professionals and where the offer of training is higher. These factors may contribute to a difference in Pap test analysis among MHDI groups.

In medium-MHDI municipalities and especially in low-MHDI municipalities, several indicators, such as transformation zone percentage, positivity index and HSIL percentage, are below recommended values, suggesting problems in the detection of severe abnormalities, which can be associated with a high number of false-negative exams, possibly related not only to the poor quality of the smear or low laboratory quality but also with problems related to program organization. Despite efforts, including external quality control of laboratories—although limited to a small number of samples in selected laboratories examined periodically (21, 22)—training of the professionals, and cervical cancer prevention campaigns, among others, the results suggest that the opportunistic cervical cancer screening program is not effective, especially in underdeveloped regions in Brazil.

In addition to the factors influencing the quality of the screening test, one should also consider the possible influence of healthcare barriers, such as difficulties in access to public health services, lack of knowledge, illiteracy, and sense of embarrassment (23, 24). These barriers are more present in underdeveloped regions and could possibly affect the percentage of abnormal lesions.

HDI is associated with a cancer prognosis (25) and is inversely associated with the incidence of and mortality from cervical cancer (26). An increase of 0.2 is the HDI was associated with a 20% decrease in the risk of developing cervical cancer and a 33% decrease in the risk of dying of cervical cancer (27). A recent study using Brazilian hospital-based cancer registry data from 2005 to 2014 shows that the stage at diagnosis was associated with HDI, with a significant association between low HDI and a smaller proportion of cases diagnosed at an early stage (28). Therefore, it is important to consider the MHDI when defining and implementing cervical cancer screening strategies in Brazil.

The future policies of cervical cancer screening programs in Brazil should include the introduction of molecular tests with the purpose of detecting infection with high-risk types of the human papillomavirus (hr-HPV). The hr-HPV test has already been introduced in several cervical cancer screening programs due to the intrinsic limitation of the cytological test or the heterogeneous quality offered by diagnostic services. Studies have shown that the hr-HPV test has higher sensitivity and negative predictive value for detecting intraepithelial lesion neoplasia 2 or worse (CIN2$^+$) compared with either conventional or liquid-based cytology (29–31). Hence, possible changes in the cervical cancer screening program in Brazil can include the use of hr-HPV testing as a primary screening test. The scheme to be used should consider the different socioeconomic contexts of Brazil (different levels of MHDI) and the recommendation to be applied for each model (e.g., interval recommendation). A recent study suggested sample self-collection and HPV testing as a promising strategy for unscreened or underscreened women who are unwilling or unable to undergo clinic-based cervical screening (32). This scheme is useful for women living in remote areas or in areas where access to primary care attention is difficult. Finally, another important action that could increase the coverage of screening and is an important condition for the high performance of the HPV test is the implementation of an organized population-based cervical cancer screening program.

The present study is limited by the restricted information available from SISCOLO, as SISCOLO, as already mentioned, only gives the number of exams and not the number of women who underwent the exam, includes not only first-level but also follow-up Pap tests and does not include data on Pap tests performed in the private health system. In addition, for a more comprehensive analysis of the cervical cancer screening program, other indicators, such as coverage rates, predictive

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

values, colposcopy referrals, treatment rates and screening failures, that could not be determined by the present study, should be considered.

In conclusion, this study showed that the groups of municipalities with low- and medium-MHDI have the majority of quality indicators below the values recommended by the INCA, with, in general, no improvement trend in the years under study. Although they showed slightly improved quality indicators, the majority of the group of municipalities with high MHDI present stationary trends, showing an increase only in the detection of ASC (ASC-US and ASC-H), which was also observed in the low- and medium-MHDI municipalities. The results suggest that the MHDI should be considered in the definition of the policies of the screening program for cervical cancer in Brazil and that the current program requires adjustments to achieve better efficiency.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R.F.A. Costa, F.de Lima Vazquez, L.C. Zeferino, J.H.T.G. Fregnani
Development of methodology: R.F.A. Costa, J.H.T.G. Fregnani
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.F.A. Costa
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.F.A. Costa, A. Longatto-Filho, C. Pinheiro, L.C. Zeferino, J.H.T.G. Fregnani
Writing, review, and/or revision of the manuscript: R.F.A. Costa, A. Longatto-Filho, C. Pinheiro, L.C. Zeferino, J.H.T.G. Fregnani
Study supervision: J.H.T.G. Fregnani

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 14, 2019; revised October 13, 2019; accepted December 6, 2019; published first December 13, 2019.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação Geral de Ações Estratégicas. Divisão de Apoio à Rededе Atenção Oncológica. Diretrizes Brasileiras para o Rastreamento do Câncer do Colo do Útero. Rio de Janeiro: INCA; 2011.
3. Costa RF, Longatto-Filho A, Pinheiro C, Zeferino LC, Fregnani JH. Historical analysis of the Brazilian Cervical Cancer Screening Program from 2006 to 2013: a time for reflection. PLoS ONE 2015;10:e0138945.
4. Alves Costa RF, Longatto-Filho A, Vazquez FdL, Pinheiro C, Zeferino LC, Tavares Guerreiro Fregnani JH. Trend analysis of the quality indicators for the Brazilian cervical cancer screening programme by region and state from 2006 to 2013. Bmc Cancer 2018;18:126.
5. Brasil. Programa das Nações Unidas para o Desenvolvimento (PNUD). Instituto de Pesquisa Econômica Aplicada (Ipea). Fundação João Pinheiro (FJP). Atlas do Desenvolvimento Humano no Brasil 2013. Brasilia: PNUD; 2013.
6. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Programa Nacional de Controle do Câncer do Colo do Útero. Rio de Janeiro: INCA; 2011.
7. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19:335–51.
8. Freitas RA, Carvasan GA, Morais SS, Zeferino LC. Excessive Pap smears due to opportunistic cervical cancer screening. Eur J Gynaecol Oncol 2008;29:479–82.
9. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Monitoramento das ações de controle dos cânceres do colo do útero e de mama. Bol INF Deteção Precoce. Rio de Janeiro: INCA; 2014.
10. Discacciati MG, Barboza BM, Zeferino LC. [Why does the prevalence of cytopathological results of cervical cancer screening can vary significantly between two regions of Brazil?]. Rev Bras Ginecol Obstet 2014;36:192–7.
11. Thuler LSC, Zardo LM, Zeferino LC. Perfil dos laboratórios citopatológicos do Sistema Único de Saúde. J Bras Patol Med Lab 2007;43:12.
12. Bortolon PC SM, Corrêa FM, Dias MBK, Knupp VMAO, Assis M, Claro IB. Avaliação da Qualidade dos Laboratórios de Citopatologia do Colo do Útero no Brasil. [Evaluating the quality of cervical cytopathology laboratories in Brazil]. Rev Bras Cancerol 2012;58:435–44.
13. Manrique EJC, Tavares SBdN, Souza NLA, Albuquerque ZBP, Zeferino LC, Amaral RGU. A revisão rápida de 100% é eficiente na detecção de resultados falsos-negativos dos exames citopatológicos cervicais e varia com a adequabilidade da amostra: uma experiência no Brasil. Rev Bras Ginecol Obstet 2007;29:402–7.
14. Franco R, Amaral RG, Montemor EBL, Montis DM, Morais SS, Zeferino LC. Fatores associados a resultados falso-negativos de exames citopatológicos do colo uterino. Rev Bras Ginecol Obstet 2006;28:479–85.
15. Pinho-Franca JR, Chein M, Thuler LCS. Patterns of cervical cytological abnormalities according to the Human Development Index in the northeast region of Brazil. BMC Womens Health 2016;16:54.
16. Amaral RG, Manrique EJC, Guimarães JV, Sousa PJd, Mignoli JRQ, Xavier AdF, et al. Influência da adequabilidade da amostra sobre a detecção das lesões precursoras do câncer cervical. Rev Bras Ginecol Obstet 2008;30:556–60.
17. Eversole GM, Moriarty AT, Schwartz MR, Clayton AC, Souers R, Fatheree LA, et al. Practices of participants in the college of american pathologists interlaboratory comparison program in cervicovaginal cytology, 2006. Arch Pathol Lab Med 2010;134:331–5.
18. Wright TC Jr., Stoler MH, Behrens CM, Sharma A, Sharma K, Apple R. Interlaboratory variation in the performance of liquid-based cytology: insights from the ATHENA trial. Int J Cancer 2014;134:1835–43.
19. Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Estimativas 2018: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2018.
20. Organización Panamericana de la Salud (OPS). Módulo de citologia: procedimientos. Washinton D.C.:OPS; 2000.
21. Azara CZ, Manrique EJ, Tavares SB, de Souza NL, Amaral RG. Internal quality control indicators of cervical cytopathology exams performed in laboratories monitored by the external quality control laboratory. Rev Bras Ginecol Obstet 2014;36:398–403.

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

22. Freitas HGd, Thuler LCS. Monitoramento externo da qualidade dos exames citopatológicos cervicais realizados pelo Sistema Único de Saúde (SUS) no Estado de Mato Grosso do Sul. Rev Bras Ginecol Obstet 2012;34:351–6.
23. Albuquerque CL, Costa Mda P, Nunes FM, Freitas RW, Azevedo PR, Fernandes JV, et al. Knowledge, attitudes and practices regarding the Pap test among women in Northeastern Brazil. Sao Paulo Med J 2014; 132:3–9.
24. Navarro C, Fonseca AJ, Sibajev A, Souza CI, Araujo DS, Teles DA, et al. Cervical cancer screening coverage in a high-incidence region. Rev Saude Publica 2015;49:17.
25. Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet 2012;380: 1840–50.
26. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the human development index (2008-2030): a population-based study. Lancet Oncol 2012;13:790–801.
27. Singh GK, Azuine RE, Siahpush M. Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development. Int J MCH AIDS 2012;1:17–30.
28. Vale DB, Sauvaget C, Muwonge R, Thuler LCS, Basu P, Zeferino LC, et al. Level of human development is associated with cervical cancer stage at diagnosis. J Obstet Gynaecol 2019;39:86–90.
29. Schiffman M. Integration of human papillomavirus vaccination, cytology, and human papillomavirus testing. Cancer 2007;111:145–53.
30. Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ 2008;337:a1754.
31. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518–27.
32. Castle PE, Silva VRS, Consolaro MEL, Kienen N, Bittencourt L, Pelloso SM, et al. Participation in cervical screening by self-collection, Pap, or a Choice of Either in Brazil. Cancer Prev Res 2019;12:159–70.

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.

Published OnlineFirst December 13, 2019; DOI: 10.1158/1940-6207.CAPR-19-0306

AACR American Association for Cancer Research

Cancer Prevention Research

The Quality of Pap Smears from the Brazilian Cervical Cancer Screening Program According to the Human Development Index

Ricardo Filipe Alves Costa, Adhemar Longatto-Filho, Fabiana de Lima Vazquez, et al.

Cancer Prev Res 2020;13:299-308. Published OnlineFirst December 13, 2019.

Updated version	Access the most recent version of this article at: doi:10.1158/1940-6207.CAPR-19-0306
Supplementary Material	Access the most recent supplemental material at: http://cancerpreventionresearch.aacrjournals.org/content/suppl/2019/12/13/1940-6207.CAPR-19-0306.DC1

Cited articles	This article cites 26 articles, 2 of which you can access for free at: http://cancerpreventionresearch.aacrjournals.org/content/13/3/299.full#ref-list-1

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cancerpreventionresearch.aacrjournals.org/content/13/3/299. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from cancerpreventionresearch.aacrjournals.org on March 26, 2021. © 2020 American Association for Cancer Research.