

Impact of the COVID-19 Pandemic on Cervical Cancer Screening in São Paulo State, Brazil

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Keywords

COVID-19 pandemic · Cervical cancer screening · Neoplasia · Papanicolaou test

Abstract

Introduction: The early identification of precursor lesions followed by appropriate treatment prevents development of cervical cancer and its consequences. **Objective:** The present study evaluated the influence of the COVID-19 pandemic on cervical cancer screening by comparing the quantity of tests to detect cervical cellular changes performed in São Paulo state in 2019, prior to the detection of SARS-CoV-2 in Brazil, to the first (2020) and second (2021) years following its appearance. **Materials and Methods:** Data from Fundação Oncocentro de São Paulo (FOSP), the agency that analyses

approximately 220,000 Papanicolaou (Pap) tests annually, were reviewed. **Results:** A median of 1,835 Pap tests were performed in 55 municipalities in 2019. This was reduced to 815 tests in 2020, a 56% decrease ($p = 0.0026$). In 2021, the median number was 1,745, a 53% increase over 2020 levels ($p = 0.0233$). The 26 municipalities with >1,000 tests in 2020 had a median reduction from 4,433 in 2019 to 2,580 in 2020 ($p = 0.0046$). The 29 municipalities with <1,000 tests had a median reduction from 951 in 2019 to 554 in 2020 ($p < 0.0001$). There was a 44% reduction in the number of follow-up cytological evaluations from 2019 to 2020, followed by a 30% increase in the following year. However, the percentage of women with a normal finding or with any abnormality remained unchanged. The findings from a histological evaluation of women in São Paulo city indicated that the percent of cases positive for CIN-1 ($p < 0.0410$) and CIN-3

($p < 0.0012$) increased in 2020 and 2021 as compared to 2019 levels. **Conclusion:** A reduction in testing for cervical cancer in the first year of the COVID-19 pandemic, accompanied by an elevated incidence of precancerous lesions in each of the first 2 years following its initiation, may portend a subsequent increased occurrence of cervical cancer in Brazil.

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Introduction

Cervical cancer is the fourth most frequent cancer in women worldwide with an estimated 604,000 new cases in 2020. Of the approximately 342,000 deaths from cervical cancer in 2020, about 90% occurred in low- and middle-income countries (LMICs). The population of LMICs have limited access to cervical cancer detection protocols, and this malignancy is often identified only in advanced stages and with advanced symptoms. In addition, access to treatment of cancerous lesions (surgery, radiotherapy, and chemotherapy) may be limited, resulting in a higher rate of death from cervical cancer in these countries [1]. According to a World Health Organization (WHO) prediction, in the absence of success interventions there may be as many as 44.4 million cases of cervical cancer diagnosed globally over the period from 2020 to 2069, with almost two-thirds of cases occurring in LMICs. In 2018, the WHO announced a global call for action towards elimination of cervical cancer. This stimulated many LMICs, in the pre-COVID-19 period, to revise their national cancer control policies and commit resources to improve cervical cancer screening [2].

Brazil is a large country with an extensive public health system, the Unified Health System (SUS), covering 41 million women aged 25–64. Despite the free services provided by the SUS, screening for cervical cancer has not been comparable in all regions of the country and this malignancy remains a serious public health problem in some regions of Brazil, where the screening program is opportunistic. For this reason, it seems important improvements in cervical cancer screening policy are needed (including São Paulo state) as the incidence of this type of cancer remains high, with approximately 16,000 new cases expected in 2022, and an estimated global risk of 12.6 per 100,000 women (adjusted rate), ranging from 6.8 per 100,000 women in São Paulo city, São Paulo state, southeast region to 61.5 per 100,000 women in Manaus city, Amazonas state, north region of Brazil. Cervical cancer screening programs based on cytological evaluation of Papanicolaou (Pap) tests have substantially reduced

cervical cancer incidence and mortality in countries that implemented an organized program for cancer screening. Current Brazilian National Guidelines recommend screening with a Pap test every 3 years after two consecutive negative annual results in the 25–64 age group [3]. This early diagnosis, followed if necessary, by colposcopy, histological analyses, and treatment of precursor lesions, is essential for the prevention of advanced disease in the female population. The Pap test has been accredited as effective, safe, and a low-cost public strategy for early detection of this cancer when properly introduced by public health authorities [4]; otherwise, an opportunistic system may be insufficient for cervical injury reduction strategies [5]. The estimated annual number of cytologies (Pap tests) performed in Brazil is 11,617,535 [5].

At the end of 2019, a novel coronavirus designated as SARS-COV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pneumonia. On 11 March 2020, the WHO officially characterized the global COVID-19 outbreak as a pandemic [6]. In Brazil, to date 661,000 deaths due to this infection have been recorded, of which 167,000 are in the state of São Paulo [7]. Public health measures to reduce virus transmission included mask wearing, social distancing, and isolation. This was accompanied by a reluctance to visit medical facilities for fear of exposure to COVID-19. Changes in the health care system due to the priority to contain the SARS-COV-2 virus culminated in delays in the screening and diagnoses of cervical lesions [7], as well as medical treatment of other disorders. Brazil ultimately experienced one of the highest rates of COVID-19 infection and deaths [8–10]. Many preventive services, routine screening activities, and elective gynecologic procedures were understandably postponed or decreased throughout the country [11]. The COVID-19 pandemic has severely affected routine human papillomavirus vaccination programs, with major decreases in the daily average total number of vaccinations reported during the national lockdown – a delay already felt in the initiative to eliminate cervical cancer [9, 10, 12–14]. Success in re-establishing human papillomavirus vaccination programs has been variable, as both high-income countries and lower income countries continue to grapple with controlling COVID-19 and returning to a state of normalcy [15–17].

The present study sought to document the possible impact of the COVID-19 outbreak on cancer screening programs in São Paulo state, specifically on interventions to detect precursor lesions and prevent development of cervical cancer. It is estimated that cancers remained undiagnosed in at least 100,000 Brazilians due to the failure

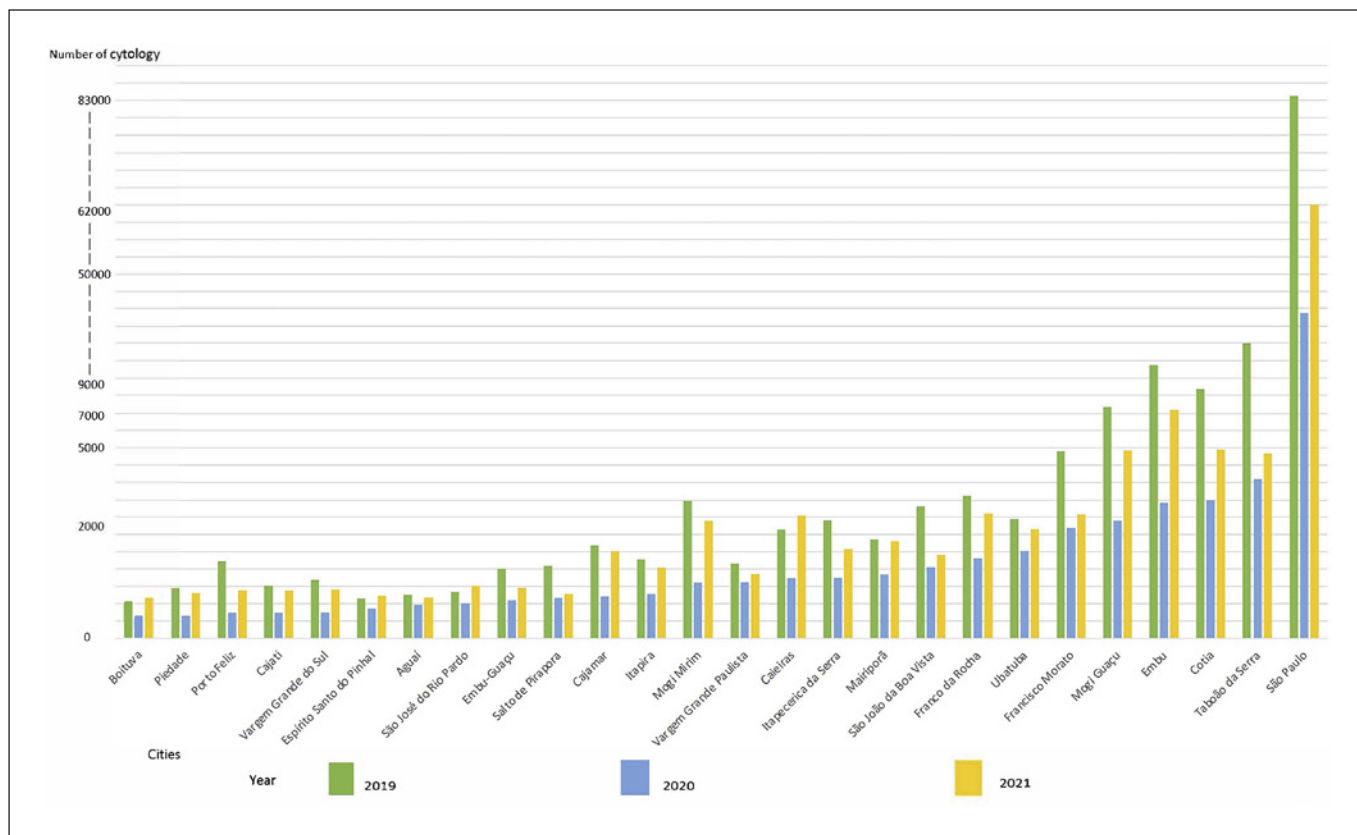


Fig. 1. Comparison of Pap tests performed in 2019, 2020, and 2021 by municipality that performed more than 1,000 exams in 2020 in the São Paulo state. SOURCE: FOSP.

to perform effective testing during the pandemic [8, 10, 12]. Fundação Oncocentro de São Paulo (FOSP) works as an advisor in the formulation and conduction of health policy in the area of oncology within the state of São Paulo, prioritizing cancer prevention and control activities. Its laboratory performs approximately 220,000 Pap tests a year from 342 health units throughout the state [11]. To evaluate the effects of the SARS-CoV-2 pandemic on cervical cancer screening, a study was initiated to determine the number of visits for cervical cancer-related procedures performed by FOSP in the pre-pandemic year 2019 compared to the years 2020 and 2021.

Material and Methods

Participants consisted of women undergoing opportunistic routine cervical cancer screening performed at FOSP laboratory, São Paulo state, from January 2019 to December 2021. The number of cytopathological examinations of the cervix performed in 55 municipalities in the state of São Paulo in 2019, prior to the detection of SARS-CoV-2 in Brazil, with the numbers performed in

2020, the first year of the pandemic, and in the subsequent year, 2021, were compared. The inclusion criterion was verification of the date of a cytological cervical examination and the presence of a written evaluation in women of all ages. The exclusion criterion was the absence of validation of the time of a cervical examination or its assessment. Informed consent was deemed to not be necessary due to the secondary nature of the evaluations.

Statistics

The differences in the number of examinations performed between 2019 and 2020, and between 2020 and 2021, were evaluated by the Mann-Whitney test. Values were reported as median (interquartile range). Differences in the outcomes of histological evaluations over the 3-year time period were analysed by Fisher's exact test. A *p* value <0.05 was considered significant.

Results

The change in the number of Pap tests performed in the state of São Paulo between the years 2019, 2020, and 2021 is shown in Table 1. In the 55 municipalities included, a median of 1,835 Pap tests were performed in 2019.

Table 1. Change in the number of PAP smear examinations performed in Brazilian municipalities (São Paulo state) between 2019 and 2021.

Exam volume in 2020	Municipalities evaluated, <i>n</i>	Median examinations recorded (IQR)		
		2019	2020	2021
All	55	1,835 (922, 4,301) ^a	815 (545, 2,568)	1,745 (777, 3,852) ^b
>1,000	26	4,433 (2,632, 7,105) ^c	2,580 (1,501, 4,307)	3,934 (2,204, 5,735) ^d
<1,000	29	951 (564, 1,451) ^e	554 (304, 730)	817 (460, 11,326) ^f

^a*p* = 0.0026 versus 2020. ^b*p* = 0.0233 versus 2021. ^c*p* = 0.0046 versus 2020. ^d*p* = 0.0266 versus 2020. ^e*p* < 0.0001 versus 2020. ^f*p* = 0.0021 versus 2020. All comparisons are by the Mann-Whitney test.

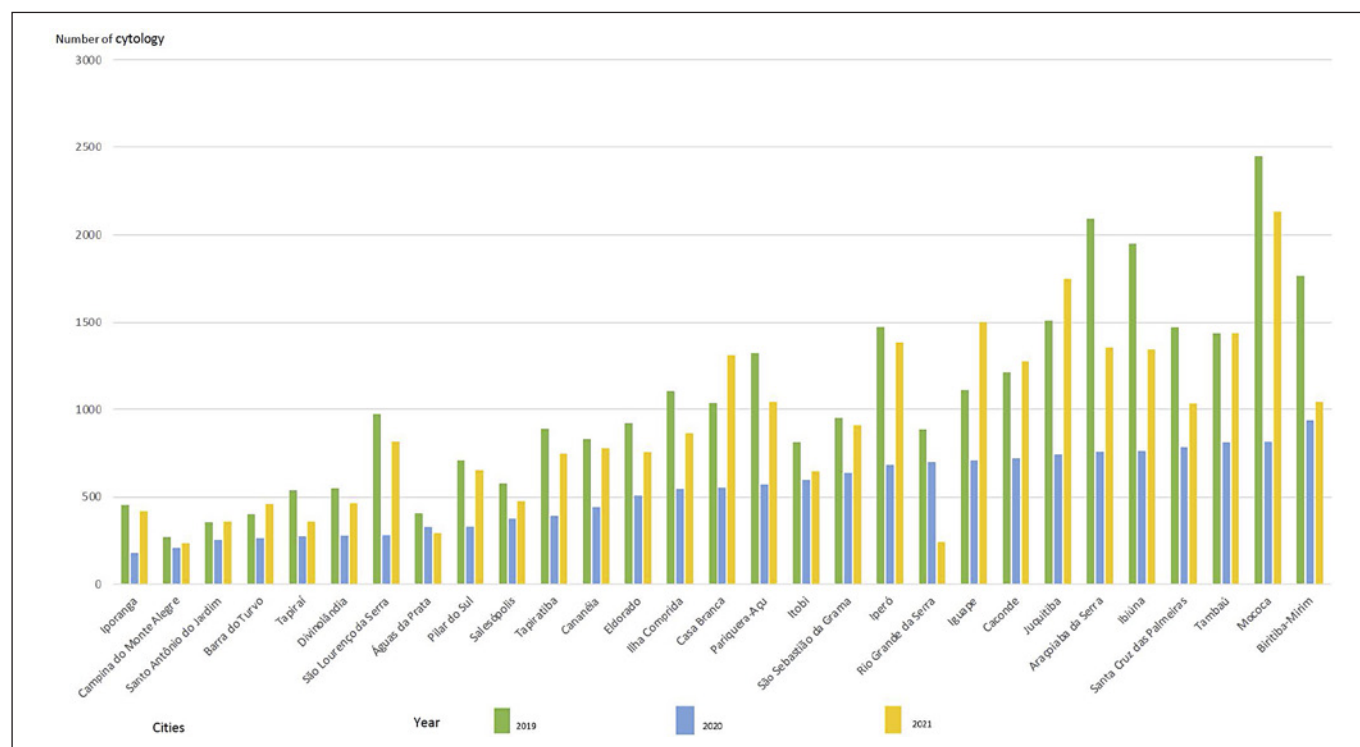


Fig. 2. Comparison of Pap tests performed in 2019, 2020, and 2021 by municipality that performed less than 1,000 exams in 2020 in the São Paulo state. SOURCE: FOSP.

This decreased to 815 in 2020, a 56% reduction ($p = 0.0026$). In 2021, the median number of tests increased by 53%–1,745 ($p = 0.0233$). In municipalities that performed >1,000 Pap exams in 2020, the number of tests declined from 2019 to 2020 ($p = 0.0046$) and then increased in 2021 over 2020 levels ($p = 0.0266$). Similarly, in municipalities that performed <1,000 Pap exams in 2020 the number of tests declined from 2019 to 2020 ($p < 0.0001$) and then increased in 2021 over 2020 levels ($p = 0.0021$). The number of tests performed in 2021 was comparable to the 2019 level in both the high ($p = 0.3584$) and low ($p = 0.2980$)

volume municipalities. The number of Pap tests performed in each individual municipality over the 3-year period is shown graphically in Figures 1, 2. The changes in test numbers for each municipality are presented in online supplementary Tables 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000529249).

The findings from cytological examinations performed in 2019, 2020, and 2021 in all municipalities are shown in Table 2. While the total number of women evaluated was reduced in 2020 as opposed to 2019 levels, and subsequently increased again in 2021, there were no differences in the

Table 2. Cytology results in Brazilian municipalities (São Paulo state) between 2019 and 2021

Result	Cases, n (%)		
	2019 (N = 244,850)	2020 (N = 137,688)	2021 (N = 195,799)
Negative	236,028 (96.4)	132,685 (96.4)	188,146 (96.1)
ASC-US	4,480 (1.8)	2,250 (1.6)	3,373 (1.7)
AGUS	603 (0.25)	390 (0.28)	798 (0.41)
ASC-H	1,245 (0.51)	761 (0.55)	1,170 (0.60)
LSIL	1,873 (0.76)	1,181 (0.86)	1,629 (0.83)
HSIL	587 (0.24)	403 (0.29)	655 (0.33)
Carcinoma	34 (0.013)	18 (0.013)	28 (0.014)

ASC-US, atypical squamous cells of unknown significance; AGUS, atypical glandular cells of unknown significance; ASC-H, atypical squamous cells that may be HSIL; LSIL, low-grade squamous intraepithelial cell lesion; HSIL, high-grade intraepithelial cell lesion.

percentage of cases with a negative evaluation (96%), as well as in those with various abnormalities over the 3-year time interval.

The results of histological examinations performed over the 3-year study period from the city of São Paulo, the municipality with the majority of cases, are presented in Table 3. Histological findings from the other municipalities were incomplete or too few to analyse. There were 2,469 examinations in São Paulo city in 2019, a 58% decrease to 1,046 in the year 2020 following by a small 15% increase to 1,223 in 2021. The percentage of the cases that were CIN-1 increased from 8.1% in 2019 to 10.1% in 2020 and 10.1% in 2021 ($p \leq 0.0493$ vs. 2019). Similarly, the percentage of cases with a diagnosis of CIN-3 increased from 1.9% in 2019 to 4.5% in 2020 and 3.8% in 2021 ($p \leq 0.0012$ vs. 2019).

Discussion

In the state of São Paulo, the number of Pap tests, as well as the number of histological evaluations performed in the city of São Paulo at FOSP laboratory, decreased during the first year of the COVID-19 pandemic (2020) as compared to the previous year (2019). In addition, according to data from Secretary of State for Health of São Paulo, from 2008 to 2019 the average rate of the female population coverage was approximately 75% in the target population (SUS). Also, the number of Pap tests has been

Table 3. Histological diagnoses in the city of Sao Paulo between 2019 and 2021

Diagnosis	Cases, n (%)		
	2019 (N = 2,469)	2020 (N = 1,046)	2021 (N = 1,223)
Benign/negative	2,053 (83.2)	803 (76.8)	950 (77.7)
HPV+	30 (1.2)	16 (1.5)	19 (1.6)
CIN-1	199 (8.1) ^a	106 (10.1)	124 (10.1)
CIN-2	117 (4.7)	59 (5.6)	72 (5.9)
CIN-3	48 (1.9) ^b	47 (4.5)	46 (3.8)
Invasive carcinoma	15 (0.61)	8 (0.76)	8 (0.65)
Other carcinomas*	7 (0.28)	7 (0.67)	4 (0.33)

HPV+, human papillomavirus positive; CIN-1,2,3, cervical intraepithelial neoplasias of increasing severity. *Microinvasive squamous cell carcinoma, adenocarcinoma in situ, mucinous adenocarcinoma, glandular adenocarcinoma. ^a $p = 0.0493$ versus 2020, 0.0410 versus 2021. ^b $p = 0.0001$ versus 2020, 0.0017 versus 2021.

decreased to 16.7% in the same period over the years from 1.96 to 1.64 million exams. In 2020, in the pandemic outbreak epicentre, the coverage of Pap tests was 38% totalizing 1.22 million exams [18].

However, according to FOSP data, in the second year of the pandemic (2021) the number of Pap tests returned to the pre-pandemic frequencies. Thus, similar to previous concerns about the negative influence of the pandemic on efforts by the public health system to increase participation in testing for the early stages of abnormalities leading to cervical cancer [4, 9] this testing also decreased in Brazil. This undoubtedly was due to a number of factors, including women's reluctance to visit public health clinics and risk exposure to SARS-CoV-2 plus the need to reassign professional and technical staff to the more urgent task of mitigating the influence of the pandemic on the local population. Fortunately, at least for the population in the present study, this decrease in Pap testing and cytological evaluations was only transitory and returned the following year to pre-pandemic levels. This indicates that despite being in the midst of a terrifying pandemic, women resumed their scheduled visits for gynaecological examinations.

The percentage of cases positive for CIN-1 and CIN-2 increased in the city of São Paulo in each of the first 2 years following the pandemic outbreak. One can speculate that this occurred because, although the cytological detection of these lesions occurred in 2019, their histopathological analyses were not performed until 2020 and 2021. Thus, while the total number of cytology tests decreased

post-pandemic outbreak, the need for follow-up evaluations of abnormal cases resulted in an increased rate of lesion detection.

Recently, Ribeiro and colleagues proposed a reengineering of the Brazilian health infrastructure, enriching programs to reduce disparities in cervical cancer incidence and mortality during the COVID-19 pandemic [17]. Effective screening programs require multidisciplinary integration and government commitment to introduce clinical-laboratory tools that effectively improve the detection and consequences of a cervical cancer diagnosis. A major concern that remains to be determined is to optimize the recruitment of women whose cervical lesions were detected by the Pap test in the first year of the pandemic to assure that they will return to be biopsied and receive further medical care. Mayo and colleagues published an elegant meta-analysis analysing patients screened for preventable cancers in the time intervals before and during the COVID-19 pandemic. Taking all cases, the authors found a significant reduction in the incidence ratios during the COVID-19 pandemic for breast cancer, colon cancer, and cervical cancer, potentially negatively impacting morbidity and mortality [19]. As documented by International Agency for Research on Cancer (IARC), many LMICs have chronic limitations in their ability to efficiently prevent cervical cancer and need to introduce more effective programs for screening. The worldwide impact of COVID-19 on cervical cancer screening and diagnosis of its precursor lesions will only be recognized after each country undergoes a comprehensive evaluation of its screening program [9].

In conclusion, the decline in cervical cancer screening in Brazil during the first year of the COVID-19 pandemic, followed by an increased rate of cervical abnormalities identified by histological evaluations in the first 2 years of the pandemic, indicates that the incidence of cervical cancer in Brazilian women is likely to increase. The current study was limited by the missing information about the follow-up of many women identified as having high-grade cervical lesions and also due to the lack of results from colposcopic analyses and biopsies of some cases. The maintenance of constant evaluations and similar investigations to the present study may provide robust data to optimize the planning of strategies that are more adequate for this screening.

Acknowledgment

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Statement of Ethics

This study protocol was reviewed and approved by *Comitê de Ética em Pesquisa do Instituto Adolfo Lutz/Secretaria de Saúde do Governo do Estado de São Paulo*, approval number: 5.751.873, CAAE: 60891622.1.0000.0059. A written informed consent was not required (according to national guidelines).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary materials. Further enquiries can be directed to the corresponding author.

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