Organization of cervical cancer screening with DNA−HPV testing impact on early−stage cancer detection: a population−based demonstration study in a Brazilian city

Julio Cesar Teixeira, Diama Bhadra Vale Cirbia Silva Campos Joana Froes Bragança Michelle Garcia Discacciati and Luiz Carlos ZeferinoFull Professor*

Department of Obstetrics and Gynecology, University of Campinas (UNICAMP), Campinas, SP, Brazil

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Summary

Background Cervical cancer is a preventable disease, and the Brazilian screening is opportunistic and has low impact. The current study evaluated an initiative to organize screening using DNA−HPV testing as a replacement for cytology.

Methods This demonstration study examined information from 16 384 DNA−HPV tests for screening in women aged 25−64 years from Indaiatuba city between October 2017−March 2020. The comparison was 20 284 women screened using cytology between October 2014−March 2017. The flowchart indicates the repetition of a negative test in five years. HPV16- and/or HPV18-positive tests and the 12 pooled high−risk HPV-positive tests with abnormal liquid−based cytology were referred for colposcopy. If cytology was negative, the HPV test was repeated in 12 months. The analyses evaluated coverage, age−group compliance, and cancer detected.

Findings After 30 months, the coverage projection was greater than 80%. The age compliance for the HPV test was 99.25%, compared to 78.0% in the cytology program. The HPV test program showed 86.8% negative tests and 6.3% colposcopy referrals, with 78% colposcopies performed. The HPV testing program detected 21 women with cervical cancer with a mean age of 39.6 years, and 67% of cancers were early−stage compared to 12 cervical cancer cases detected by cytological screening (p=0.0284) with a mean age of 49.3 years (p=0.0158), and one case of early −stage (p=0.0014).

Interpretation Organizing cervical cancer screening using DNA−HPV testing demonstrated high coverage and age compliance in a real−life scenario, and it had an immediate impact on cervical cancer detection at an early−stage.

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Keywords: cervical cancer; Papillomavirus infections; public health; cancer screening; Pap smear, DNA-HPV test

Introduction

In Brazil, 16 590 new cases of cervical cancer are expected annually in the 2020−2022 triennium with a mortality rate of 6.17/100 000. These numbers indicate that cervical cancer, which is a preventable disease, causes the death of one woman every 90 minutes in Brazil.[1] Population-based screenings are essential for the early detection and treatment of precursor lesions and cervical cancer in its early−stages.[2] The Brazilian cervical cancer screening program started in 1984, and it went nationwide in 1998. The strategy is based on conventional cytology (Pap−test), which should be repeated every three years after two consecutive annual negative results in women aged 25 to 64 years.[3] The Unified Health Care System (*Sistema Unico de Saude*, SUS) offers this test free of charge to women with a cervix who are sexually active, and it includes transsexual men and nontranssexual people binaries designated women at birth.[3] Despite the implementation of this program, Brazil's cervical cancer incidence and mortality rates have remained relatively stable for decades.[1]

*Corresponding author: Julio Cesar Teixeira. Division of Gynecologic and Breast Oncology, Women's Hospital, UNICAMP. Rua Alexander Fleming, 101 − Cidade Universitaria, Campinas (SP), Brazil. Zipcode: 13083−881
E-mail address: juliotex@unicamp.br (J.C. Teixeira).

Research in context

Evidence before this study

The literature review on the transition of opportunistic to organized programs for population screening of cervical cancer showed two gaps related to this process in low- or middle-income settings: a lack of information about organized programs and replacing conventional cytology (Pap test) with a DNA-HPV test. There is a need for real-life information for Brazil and similar countries to support actions on updating existing programs, which are costly and with a very low impact on cervical cancer mortality.

Added value of this study

This study shows the first's results of a pivotal demonstration study in a Brazilian city, started in 2017, aimed to achieve high population coverage and compliance to the guidelines using a primary DNA-HPV test. This population-based study done in a real-life scenario is one of the pioneers' studies in middle-income settings and including women aged 25-29 years.

Implications of all the available evidence

Results from this demonstration program are crucial to providing a reasonable way to implement HPV testing as a cervical cancer screening. The Program achieved high age compliance and coverage near 100%, with at least 78% of abnormal tests follow-up already done, suggesting a path to the consolidation of an organized program. After 30 months running, the Program achieved a cornerstone result: the detection of more cervical cancer cases, 67% of them at an very early-stage (microinvasive carcinoma), preceding 10 years in the diagnosis. Early-stage detection leads to treatment less costly, less mutilating, and near to 100% of the cure. These immediate results in addition to the previous of cost-effectiveness demonstration may support the Health Managers adopting the test and the Program structure to set an efficient and lasting national screening program.

Clinicians in Brazil's public and private health system follow the Brazilian Guidelines for the Screening of Cervical Cancer defined by the National Cancer Institute (INCA), Ministry of Health.[3] However, Brazil's current cervical cancer screening system is opportunistic, which means that testing follows the spontaneous demand of women with access to basic health units and other reasons. The result is an excess of cytology performed in women outside the range or with inadequate periodicity. Only 30% of cytology tests are performed according to the official guidelines, and 67% are excessive tests.[4] The data show that approximately 20% of cytology tests are performed on women under 25 years. Unfortunately, 60% of cervical cancers are diagnosed in the advanced stage even in more developed regions.[5–7]

One strategy to improve this scenario includes changing the periodic screening from opportunistic to organized, similar to some European countries that demonstrated a sustainable reduction in the cervical cancer mortality rate.[8–10] For an organized and successful screening program, the following pillars must be met: inform and mobilize the population; achieve the target population coverage goal; ensure access to diagnosis and treatment; ensure the quality of actions and continuously monitor and management actions, such as women diagnosed with cervical intraepithelial lesions in screening should be referred to a secondary unit for diagnostic confirmation and treatment, according to the established clinical guideline.[3]

Effectiveness in reducing mortality rates requires proper diagnosis and treatment of lesions in their intraepithelial phase or in the absence of frank invasion. Recent studies showed the superiority of population-based screening using the primary DNA–HPV test to detect precursor lesions.[11,12] The World Health Organization (WHO) recommends replacing the cytology–based strategy with HPV test–based screening when there are sufficient financial resources.[13] This recommendation is supported by the consolidated knowledge that cervical cancer is caused by the persistent infection of high–risk human papillomavirus (hr–HPV) in the cervix epithelium, primarily HPV16 and HPV18.[14,15]

Following the WHO recommendation, our research group started a population–based demonstration project in 2017 to raise epidemiological, cost–benefit and life gain indicators to support the transition of the current Brazilian cytology–based opportunistic screening program to an HPV–based organized screening program.

The "PREVENTIVO" program (PREvention of HPV Viruses in ENTire Indaiatuba by Vaccination and Organization of the screening) is based on primary DNA–HPV testing and was implemented in Indaiatuba, which is a medium–sized city (250 thousand inhabitants) in São Paulo State, Brazil.[16] The first step of implementation was the development of a dynamic microsimulation Markov model for cost–effectiveness analysis based on real–life costs. The results showed that HPV testing every five years was cost–effective and had a negative incremental ratio (ICER) for quality–adjusted life–year QALY gain. Also, changing from cytology to HPV testing for screening in Indaiatuba city made improved the cost effectiveness of the program.[17]

The current paper presents the initial results on coverage and compliance after the transition from the opportunistic cytology–based testing to an organized DNA–HPV testing screening program and demonstrates the immediate impact on cervical cancer detection in a real–life scenario.

Methods

The study protocol based on the PREVENTIVO program was previously published with detailed methodology, study population, eligibility criteria, flowchart management, and clinical procedures.[16] The study involved information on women between 25–64 years old who were served by the Brazilian Public Health System (SUS) while living in Indaiatuba. This city was chosen because all health care facilities are interconected, and its health information system is computerized with individual digital records. The users of the Brazilian Public Health System are the target population and comprised 50% of the 70 573 women candidates for cervical cancer screening, according to an official estimate in 2019.[18] The goal was to reach 80% coverage in the new screening program.

HPV test selection

Because a screening program based on HPV molecular testing should be previously validated to show high reproducible sensitivity for the detection high–grade squamous intraepithelial lesions or worse (HSIL+) [19], the Cobas® HPV Test (Roche Molecular Systems, Pleasanton, CA, USA) was chosen for this study. This test was previously evaluated in large clinical trials.[19,20] It simultaneously provides individual results on the highest-risk genotypes, HPV16 and HPV18, and aggregates results on the 12 other hr–HPV genotypes (types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). All genotypes were diagnosed simultaneously in one sample.

Management flowchart

Briefly, the following clinical procedures were followed according to the first result of the DNA–HPV test:

1. Negative DNA–HPV test: return after five years to repeat the test;
2. Positive HPV16 and/or HPV18 test: referral for colposcopy and biopsy if needed;
3. Positive HPV test for the 12 other hr–HPVs: liquid–based cytology performed on the same cervical sample. When the cytology was positive for any cervical abnormality (ASC–US, LSIL, HSIL, suspicious for glandular lesion, or cancer), the woman was referred for colposcopy. When the cytology was negative, the woman was told to return after 12 months to repeat the HPV test. In the PREVENTIVO program, a woman cannot be screened more than once within her screening round. We used a computer program that followed algorithms according to study protocols, which did not allow the collection of women outside the established flowchart.

All women with abnormal tests and indications for colposcopy were referred to a reference outpatient clinic. Excision of the transformation zone (ETZ) was performed when needed. Cases suspicious of cervical cancer or in a more complex clinical situation were referred to the regional gynecological cancer center located at Women Hospital of the University of Campinas, where radical surgeries, radiotherapy, and chemotherapy are performed to manage cervical cancer patients.

Follow–up

All women with abnormal screening tests, negative colposcopy evaluation, and negative 12–month DNA–HPV test returned to routine screening at a 5–year interval. If cervical intraepithelial neoplasia or cervical cancer was detected, the management and monitoring were guided by the Brazilian National Cancer Institute guidelines.[3]

Data collection and analysis

The new Program started in October 2017. All information about the participants was generated from the health information system. The research group had access to all data and worked as a quality control surveillance system of the Program's progress. All women with abnormal tests were selected and followed for compliance with the study flowchart. The final diagnosis was the worst grade of the histological evaluation of tissue obtained from colposcopy–directed cervical biopsy or ETZ. Cancer cases were staged according to the FIGO system.[21]

Cases screened between October 2017 and March 2020 (30 months and just before the pandemic's impact) were considered. For comparison, we used the same city population as a reference in the previous 30 months before implementation of the PREVENTIVO program (October 2014 to March 2017), when routine cytological screening was performed. The focus of this first evaluation was to assess coverage, age compliance and cervical cancer diagnosis.

Data analyses were performed using the chi–squared or Fisher's tests and the t–test in StatsDirect statistical software 3.0 (England, www.statsdirect.com). P–values < 0.05 were considered significant.

Ethical aspects

The research ethics committee of the University of Campinas approved this study (number 1045580, May 1, 2015). The mayor of Indaiatuba sanctioned a law instituting the HPV test as the standard for screening in 2017, which replaced conventional cytology in all public health care.[22] Therefore, the need for an informed consent form was waived. The research group accessed the electronic data from the medical records of the health information system. A spreadsheet for statistical analysis was created without the identification of the women

studied. The research team had no contact with any women.

Role of the funding source: Roche Diagnostics supported the supplies and equipment required to perform HPV testing, computer system development, two lab technicians, and a screening program coordinator. Roche did not have any involvement in the data collection, analysis, or interpretation. The researchers did not receive any payment for this study. The funders had no role in the study design, data collection, analysis, or writing of this report. All authors had full access to the study data and executed all the research steps, including writing and the decision to submit for publication.

Results

Between October 2017 and March 2020 after the implementation of the PREVENTIVO program, 16 384 DNA−HPV tests were performed in women from Indaiatuba city, with a progressive increase in population coverage over time, with a projected coverage greater than 80% of the target population of the public health care system at five years (Figure 1).

The age compliance in the screened population was 99.25% (16 261/16 384) in the DNA−HPV test program and 78.0% (15 822/20 284) in the cytology program performed in the previous 30-month period. The cytology program presented 16.7% of tests performed under 25 years of age (Table 1).

Of the 16 384 HPV tests performed, 86.8% (n= 14 228) showed negative results, and these women were told to return after five years to repeat the HPV test. There were 387 women (2.4%) who tested positive for HPV16 and/or HPV18. These women were referred directly for colposcopy. Of the 1 769 women who tested positive for the 12 other hr−HPV genotypes, 1 130 (6.9% of the total) presented negative cytology results and were told to repeat the HPV test after 12 months. A total of 639 women (3.9% of the total) presented abnormal cytology results and were referred for colposcopy. The total cytology tests performed were 1769 (10.8%), and the total number of women referred to colposcopy was 1 026 (6.3%). Colposcopy was 3.7 times more commonly indicated than the previous cytological screening program (1.7%, 344/20 284).

Of the 1 026 colposcopies indicated until January 2020, 244 women were waiting for the procedure, and there were 14 dropouts (colposcopy compliance of 78%). Table 2 describes the referral outcomes according to the screening test results. A total of 21 cervical cancer cases were detected: 15 cases (71%) were HPV16+ and/or HPV18+; and 6 cases (29%) were 12 other hr−HPV+ and Cytology+ (p=0.0009). Between seven cases of adenocarcinomas, all cases were HPV16+ and/or HPV18+ (HPV16= 3; HPV18= 2; HPV16 and 18= 2).

The 21 cervical cancer cases diagnosed in the first 30 months of the new screening program were compared with the 12 cases detected in the previous 30-month period (October 2014 to March 2017) based on conventional cytology screening. The results are shown in Tables 3 and 4.

Discussion

The PREVENTIVO screening program is based on the primary DNA−HPV test, and it showed high coverage

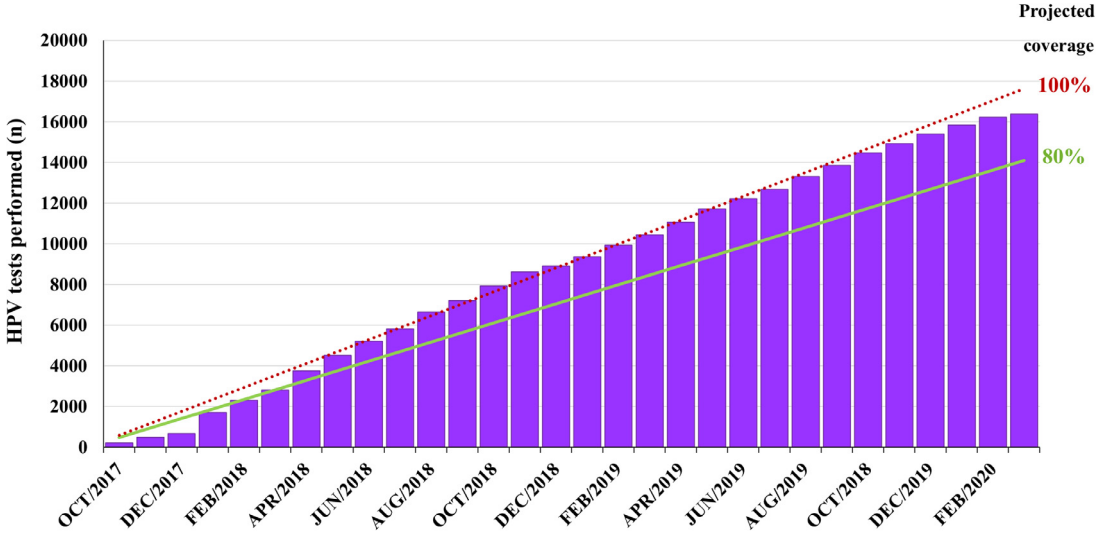

Figure 1. The cumulative number of screening HPV tests performed in the first 30 months of the program (bars; total tests = 16 384). For reference, the lines represent the projected cumulative population coverage for 5 years: 80% coverage (full/green line) and 100% coverage (dotted/red line). Population considered: public health system women users (50%) aged 25−64 years from the official 2019 population estimate [18].

	DNA−HPV test October 2017−March 2020 (n=16 384)		Cytology test October 2014−March 2017 (n=20 284)	
Age at screening	**n**	**%**	**n**	**%**
25 to 64 years (target)	16 261	***99.25***	15 822	***78.0***
< 25 years*	123	***0.75***	3 395	***16.7***
< 20 years	0	***0***	1 286	***6.3***

Table 1: Comparison of age group compliance between the* PREVENTIVO *program and the previous program based on conventional cytology.
* *67 cases in women aged 24 years.*

	Screening test result		
Outcome	**DNA−HPV16+ and/or HPV18+** (n=387)	**12 other hr−HPV+ and Cytology +** (n=639)	**Total**
Waiting for colposcopy	93	131	***224***
Dropped out	4	10	***14***
Biopsy in progress	3	8	***11***
Diagnosis completed (cervix)	287	490	***777***
Cervical cancer* (%)	***15 (5.2%)***	***6 (1.2%)***	***21 (2.7%)***
Microinvasive SCC	*7*	*5*	*12*
Microinvasive ADENO	*2*	*−*	*2*
SCC	*1*	*1*	*2*
ADENO	*5*	*−*	*5*

Table 2: Follow−up of the 1 026 colposcopy cases following an abnormal screening test.
* Chi−Squared test, p=0.0009 (cervical cancer diagnosed versus diagnosis completed). Screening test: Cobas® HPV Test (Roche Molecular Systems, Pleasanton, CA, USA); 12 other hr−HPVs encompassed types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). SCC: squamous cell carcinoma; ADENO: adenocarcinoma or adenosquamous carcinoma.

Cervical cancer diagnoses	**DNA−HPV test** October 2017−March 2020 (n=16 384)	**Cytology test** October 2014−March 2017 (n=20 284)	***P−value***
Detection (n)	21 (0.13%)	12 (0.06%)	0.0284*
Age (mean year)	39.6y	49.3y	0.0158#
Stage IA$^{\alpha}$ *vs* Stage II+ (n)	14 (67%) *vs* 3 (14%)	1 (8.3%) *vs* 8 (67%)	0.0014**
Adenocarcinoma (n)	7 (33%)	3 (25%) $^{\beta}$	0.4634**

Table 3: Cervical cancer cases were detected in a 30−month period according to the screening program based on the DNA−HPV test or conventional cytology.
* Chi−squared test
** Fisher's exact test
\# T−test.
$^{\alpha}$ Cancer staging according to FIGO[23]: Stage IA means microinvasive carcinoma; Stage II+ means Stage II or worse.
$^{\beta}$ (1) Adenosquamous carcinoma included.

and compliance rates in the targeted women (25 to 64 years old) after 30 months. It was very effective in detecting more cervical cancer cases, and 67% of these cases were at an early−stage (Stage IA), which anticipates a cancer diagnosis.

We found 21 cervical cancer cases, which suggests a higher prevalence than previously reported data.[6] Notably, these data directly reflect the implementation of an organized program using a more accurate test with higher coverage, and adequate follow-up of positively

	HPV test screening				Cytology screening			
n	Date	Age	Cervical cancer		Date	Age	Cervical cancer	
			Histology	Stage			Histology	Stage
1	JUL/19	**25**	mi−SCC	**IA1**	DEC/15	**35**	mi−ADENO	**IA1**
2	JUN/19	**27**	mi−ADENO	**IA1**	JUN/16	**36**	ADENO	**IB1**
3	MAR/19	**31**	mi−SCC	**IA1**	SEP/16	**46**	SCC	**IB1**
4	SEP/18	**34**	mi−SCC	**IA1**	NOV/15	**54**	SCC	**IB1**
5	JUN/19	**35**	mi−SCC	**IA1**	OCT/16	**37**	Adenosquamous	**IIB**
6	JAN/18	**36**	mi−SCC	**IA1**	MAY/15	**36**	SCC	**IIB**
7	DEC/18	**40**	mi−SCC	**IA1**	OCT/15	**76**	SCC	**IIB**
8	NOV/19	**40**	mi−SCC	**IA1**	JUL/15	**39**	SCC	**IIIB**
9	MAR/18	**40**	mi−ADENO	**IA1**	JUN/16	**49**	SCC	**IIIB**
10	JAN/18	**41**	mi−SCC	**IA1**	JUL/17	**61**	SCC	**IIIB**
11	FEB/18	**42**	mi−SCC	**IA1**	JAN/16	**71**	SCC	**IIIB**
12	AUG/19	**51**	mi−SCC	**IA1**	NOV/15	**52**	SCC	**IVA**
13	JAN/18	**55**	mi−SCC	**IA1**				
14	JAN/18	**44**	mi−SCC	**IA2**				
15	FEB/18	**29**	ADENO	**IB1**				
16	NOV/17	**50**	ADENO	**IB1**				
17	AUG/19	**38**	ADENO	**IB2**				
18	MAY/19	**46**	ADENO	**IB3**				
19	JUN/19	**44**	ADENO	**IIB**				
20	JUL/18	**35**	SCC	**IIIB**				
21	OCT/19	**48**	SCC	**IVA**				

Table 4: Description of cervical cancer cases in the first 30 months of the HPV test screening program compared to the previous screening using conventional cytology.
Cervical cancer staging according to FIGO;[23] mi: microinvasive; SCC: squamous cell carcinoma; ADENO: adenocarcinoma.

tested women. All of these results were found in a population without previous efficient screening. The high number of cervical cancer cases detected may be associated with a comprehensive population scan using a high-performance screening pattern, which could find cases that would appear in subsequent years after the development of symptoms. Our results support this assumption because the possible anticipation of cancer detection by 10 years, according to the average age compared to cases detected in the previous opportunistic cytological program and the high−rate detection of microinvasive carcinomas (67% vs. 8%).

The organization of the PREVENTIVO screening program suggests that the developed strategies reached a higher target population coverage and evaluated staff compliance with the program. Health professionals in this study were trained to follow the flowchart defined by the protocol. This protocol suggested the abandonment of annual screening cultures and introduced a new and more modern technique associated with patient guidance on periodicity and actions to actively search for patients targeted for screening.

The organization of a screening program is the cornerstone to significantly reduce mortality due to cervical cancer.[2] Cytology-based screening demands high-quality control of all steps, and it failed to show cost-effectiveness in the highly complex population-based programs in Europe.[23,24] The fragile health systems framework from low- and middle-income countries, where cervical cancer incidence is high, makes it challenging to overcome these barriers.[25] Notably, we detected two cases of cervical cancer in women who were outside the target age group for the cytology screening program. These women outside the target age group represent an indisputable example of the failure of the previous opportunistic screening. These data are critical and strongly support the importance of organized screening.

As a continental country, Brazil presents diverse levels of development, regions with high−middle income and other regions where poverty and inequalities prevail. The Brazilian Ministry of Health is concerned about the cervical cancer situation and spends annual resources to provide cytology tests in sufficient numbers

to cover more than 80% of the targeted population.[26] However, the effective coverage does not exceed 30% in the better scenarios.[4] Cervical cancer mortality rates have remained stable for decades and increased in the Amazon region.[1,27] Before the new program started, Indaiatuba city performed 11000 cytology tests annually in the public health system, with an estimated 33% effective coverage.

The PREVENTIVO program previously demonstrated its cost–effectiveness.[17] The present analysis is complementary and showed surprising results after the first 30 months. The program achieved high age compliance and coverage of the target population near 100%, and only 6 000 tests were performed annually, which suggests a path to the consolidation of an organized program.

Cervical cancer viral etiology analysis demonstrates the importance of stratifying the risk according to HPV genotyping. HPV16 and/or HPV18 are more related to cancer, and we detected a slightly higher number of adenocarcinomas (seven cases, all related to HPV16 and/or HPV18). When planning the program, the research team supported the city's policy-makers in implementing a single flowchart for women aged 25 to 29 years and women aged 30 years or older. We planned a specific analysis in the subgroup of women aged 25 to 29 after the end of the first round of the screening program. Additionally, the Brazilian HPV Vaccination Program started in 2014, and vaccinated women will reach the age of screening in 2025. We expect that the HPV test will be the most effective screening method for vaccinated women.[28]

Another important issue related to HPV test screening is the increasing number of colposcopies indicated. We found 3.7 times more colposcopy indications compared to the previous opportunistic screening program. It was necessary to increase the number of colposcopy professionals and update their training. An interesting new situation for them is the performing of colposcopy with knowledge of the HPV status but without information about cytology when HPV16 and/or 18 are present. Colposcopy compliance was 78%. The compliance rate in a similar implementation screening study in Argentina (2011) of 49 000 HPV tests performed between 2012–2014, was 74.6%.[29]

The transition to a high coverage program with more effective screening tests provided the detection of more cervical cancer cases, and most of them were prevalent cases. The mean age of cases was 10 years younger than the cases detected in the preceding period. A total of 67% of cases were in the very early–stage (stage IA, microinvasive) compared to the expected 9% of cervical cancers detected in stage IA in previously published regional data from 2001–2012.[6]

One of the most important factors influencing the cost–effectiveness of the program was the high cost of treating cervical cancer in advanced stages.[17] Early-stage detection leads to treatment that is less costly and less mutilating with a nearly 100% cure rate.[30] These representative numbers of early detection cases found after 30 months of the HPV test are encouraging. This result is another cornerstone in achieving an organized program, which was observed in other successful population-based programs. We considered that these achievements would have a significant impact on the survival and quality of life of these women.

There are still some activities for the PREVENTIVO program to evolve and establish itself as an organized program. It is crucial to demonstrate high coverage and compliance with program guidelines at the end of the first round and beyond. The program foresees the implementation of call and recall systems to invite the target women and follow women with abnormal tests. Periodic revisits are predicted. From the second round onwards, the demonstration of infrequent observations of new cervical cancer cases will be crucial to confirm the program's success.

The main strength of the current study is that this is the first demonstration of a population-based program to replace conventional cytology with a DNA–HPV test for primary screening in a real–life scenario in the Brazilian public health system. The results support the adoption of the test and the program structure by the Ministry of Health to set new procedures for a national screening program. The results presented are impactful, even with the short program running time.

The main limitation in replicating this program is the initial investment in the acquisition of HPV tests and the need for a digital network to record information, because the existence of a single and integrated register platform is crucial for identifying the targeted population. The PREVENTIVO program is based on all users of the Brazilian Public Health System, and it excludes users of private clinics, who correspond to approximately 50% of the total population of 25–64-year-olds.

In summary, the implementation of an organized cervical cancer screening program with DNA–HPV testing in a Brazilian city demonstrated high coverage and age compliance in a real–life scenario, and it had an immediate impact on cervical cancer detection at an early–stage. The program's actions are likely reproducible in similar locations, where the burden of this preventable cancer is high.

Contributors

JT, DV, CC, JB, and LZ developed the research protocol. JT, CC, MD, and JB working to collect the data. JT, DV, MD, and LZ coordinated the analysis and the development of this manuscript. All authors had the opportunity to review it.

Data sharing

The dataset from this study will be safely stored following the principles of research ethics. Upon completion of the study, data may be made available by the corresponding author (juliotex@unicamp.br) upon request with justification.

Declaration of interests

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lana.2021.100084.

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