LEWIS FLETCHER BUSS

Acesso à colposcopia diagnóstica entre mulheres com exame de rastreamento de câncer do colo uterino alterado no estado de São Paulo, Brasil

Dissertação apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Mestre em Ciências

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À minha família

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Buss L.F *Acesso à colposcopia diagnóstica entre mulheres com exame de rastreamento de câncer do colo uterino alterado no estado de São Paulo, Brasil* [Dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2021.

OBJETIVO**:** Investigar a taxa de aderência à colposcopia, e fatores associados com a mesma, em mulheres com lesões do colo uterino identificadas por rastreamento em serviços de atenção primária no estado de São Paulo. MÉTODOS**:** Nós analisamos duas fontes de dados. Primeiro, analisamos uma coorte prospectiva de mulheres com infeção do colo uterino pelo papilomavírus humano de alto risco (hr-HPV). A coorte foi formada em um estudo piloto da implementação de rastreamento por testagem de hr-HPV. Nós determinamos a taxa de comparecimento para colposcopia e investigamos covariáveis associadas usando regressão logística. Segundo, analisamos dados administrativos, provenientes do estado de São Paulo no Sistema de Informação do Câncer do Colo do Útero (SISCOLO) que contém os resultados de citolgia, e no Sistema de Informação Ambulatorial (SIA-SUS) em que há registros de colposcopias. Nós desenvolvemos uma rotina de *linkage* probabilístico para combinar os dois bancos de dados e determinar a taxa de acesso à colposcopia. RESULTADOS**:** Entre 1537 mulheres que testaram positivas para hr-HPV, 1235 (80,4%) compareceram para colposcopia, com uma defasagem mediana entre exame de rastreamento e colposcopia de 132 dias. Idade mais jovem (0<0,001) e resultado citológico negativo (P=0,025) foram associados com taxa menor de colposcopia. Mulheres cadastradas em unidades de saúde que ofereceram ambos o exame de hr-HPV e colposcopia tinham uma taxa de colposcopia maior comparado com aquelas que foram encaminhadas para serviços externos (788/862 [91,4%] *versus* 447/675 [66,2%], P<0.001). Usando os dados administrativos do SISCOLO e SIA-SUS, 1761 mulheres com citologia alterada foram identificadas entre 1 maio 2014 e 30 de junho 2014. 700 (39,8%) delas com um registro de colposcopia no tempo de seguimento. A taxa de colposcopia foi ligeiramente mais alta entre mulheres residentes na região metropolitana de São Paulo comparado com o interior. CONCLUSÃO**:** Perda de seguimento de mulheres com indicação de colposcopia pode comprometer o sucesso tanto do programa atual de rastreamento por Papanicolaou quanto de programas no futuro usando testagem de hr-HPV no Brasil.

Descritores: Rastreamento; Neoplasias do colo uterino; Colposcopia; Serviços de saúde; Atenção primária; Aderência

ABSTRACT

Buss L.F. *Access to diagnostic colposcopy among women with abnormal cervical screening tests in the state of São Paulo, Brazil* [dissertation]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2021.

OBJECTIVE: To investigate the rate of, and factors associated with, colposcopy attendance among women with screen-detected cervical lesions in primary care services in the state of São Paulo. METHODS: Firstly, we analyzed a prospective cohort of women positive for high risk HPV (hr-HPV) undergoing cervical cancer screening in primary care services in the municipality of São Paulo, as part of a pilot study of this screening technology. We determined the rate of attendance for colposcopy and examined co-variates associated with attendance within a logistic regression framework. Second, we analyzed state-level screening data recorded in the Sistema de Informação do Câncer do Colo do Útero, SISCOLO, which contains all cytology results performed within the public health system, and the Sistema de Informação Ambulatorial, SIA-SUS, which contains all the colposcopies. We developed a probabilistic linkage algorithm to combine these two data sources and determine the rate of colposcopy attendance among women with a cytological indication. RESULTS: Of 1537 hr-HPV-positive women, 1235 (80.4%) attended for colposcopy, with a median time from primary test to colposcopy of 132 days. Younger age (P<0.001) and concurrent negative cytology results (P=0.025) were associated with lower attendance. Women registered at units providing both the primary test and colposcopy were more likely to attend than those at units making external referrals (788/862 [91.4%] versus 447/675 [66.2%], P<0.001). Using the linked administrative datasets, we found 1761 women with abnormal cytology results between 1st May 2014 and 30th June 2014. 700 (39.8%) linked to a colposcopy record within the follow-up period. Slightly higher attendance was seen in women living in the metropolitan region of greater São Paulo compared to residents of the rest of the state. CONCLUSIONS: Non-attendance for colposcopy may limit the success of screening of current screening programs based on Papanicolaou cytology or future programs using hr-HPV testing in Brazil.

Key words: Screening; Uterine cervical neoplasms; Colposcopy; Health services; Primary care; Adherence

INTRODUCTION

Screening is the process of identifying and diagnosing disease in individuals without symptoms[1]. It involves applying a diagnostic test – be that imaging, laboratory or clinical exam – to identify a disease process in its early, so-called *pre-clinical,* state[1]. Early diagnosis can allow for early treatment and better prognosis. Although intuitively appealing, few diseases are amenable to screening, and strong evidence of benefit is needed to justify exposing ostensibly healthy, asymptomatic people to potentially harmful medical testing and risk of overdiagnosis[2].

Wilson and Jungner wrote in their classical 1986 text on screening, published by the World Health Organization, that the target condition should be important to public health, have a well-described natural history and progression from pre-symptomatic to overt disease, and be treatable[1]. The prototypical condition meeting these criteria is cancer of the uterine cervix, currently the fourth cause of cancer death among women globally[3]. This sexually transmitted cancer has a long, pre-malignant phase, the cervical epithelium first being infected by high-risk human papilloma virus (hr-HPV), before progressing through worsening dysplasia to overt malignancy, over approximately 10 years[4]. This phase, in which symptoms are not manifest, can be identified through screening[5], either by detection of dysplastic cells or hr-HPV. It is then amenable to treatment[6].

Cervical cancer screening is universally recommended by national and international bodies[5,], and the considerable decline in mortality globally[8] has been attributed partly to successful national screening programs[9]. There is, however, great variation in disease burden between countries, with 87% of deaths caused by cervical cancer occurring in developing countries[10]. Brazil is among the countries of intermediate incidence, with 17.1 cases per 100,000 women (adjusted for age) in the 2018-2019 biennial period[11]. However, this belies significant domestic disparities. For example, the age-adjusted incidence of cervical cancer was 47.3 per 100,000 women in Amazonas state, compared to 6.7 per 100,000 in São Paulo state, in the same period[11]. The differences are thought to be due, in part, to variation in screening coverage and quality.

In Brazil, cervical cancer screening with triennial Papanicolaou smears is offered opportunistically to women between the ages of 25 and 64 years by the universal health

service (Sístema Nacional de Saúde, SUS)[7]. Population coverage with the Papanicolaou smear has consistently been estimated to be high[12-14]. Based on interviewee self-reports in the national health survey (Pesquisa Nacional de Saúde)[12] and extrapolating from aggregate data[14] on the total number of smears performed, over 80% of the eligible female population is up-to-date with cervical cancer screening. According to data compiled by the International Institute of Research on Cancer, these figures place Brazil ahead of all other countries for which data are available on population coverage with a primary screening test[15]. Given that screening is a key determinate of cervical cancer mortality[11], this raises the question of why cervical cancer mortality remains relatively elevated in Brazil, despite excellent population coverage with smear-based screening.

Part of the answer may lie with issues downstream of the primary screening test. Once the presence of dysplastic cells (of hr-HPV) has been identified, further investigations is required, typically by colposcopy[7]. At colposcopy, areas of abnormal tissue can be identified by direct visualization of the cervix and application of iodine solution. Tissue biopsy of concerning regions allows definitive histologic diagnosis, be that of cervical intraepithelial neoplasia, or frank cancer. Treatment is then determined based on the histological findings, and in some case, further imaging studies[4]. If this chain of care were to break down, then the benefit of screening would be undone. In the following Master's thesis, we explore whether access to colposcopy screening, following an abnormal primary screening test, might represent a bottle neck in the chain of care.

In order to address this question, we used two data sources. First, we analyzed results from a pilot screening program that was trialing the implementation of hr-HPV-based screening in the municipality of São Paulo western and southern districts[16]. Although screening with liquid based cytology and polymerase chain reaction for hr-HPV provides important benefits over the Papanicolaou smear, this technology is not available within the national screening program in Brazil[17]. Women aged over 25 presenting to primary care services for cervical cancer screening were offered testing for hr-HPV. All hr-HPV-positive women were referred for diagnostic colposcopy[16]. We determine the absolute rate of attendance for colposcopy and identify individual- and system-level correlates of attendance.

These results are somewhat limited in that they represent an idealized situation within a research study of a novel technology. In order to gain a better understanding of the true level

of access to colposcopy within routine screening services, we next analyzed data from two administrative databases – the Sistema de Informação do Câncer do Colo do Útero, SISCOLO, and the Sistema de Informação Ambulatorial, SIA-SUS. The SISCOLO contains information on all smear test performed on the SUS. The SIA-SUS is database of ambulatory procedures, including colposcopies, that is used for billing purposes. Unfortunately, neither information system is organized at the level of the individual woman, but instead at the level of the procedure (smear or colposcopy). Furthermore, no consistent unique identifier is recorded in both datasets[18]. As such, to consolidate information at the individual woman level, it was necessary to perform a probabilistic linkage, both within and across datasets. We developed and validated a probabilistic linkage algorithm for this purpose. This allowed us to identify a cohort of women with abnormal smear results, and indication for colposcopy, and to determine the frequency of attendance for this diagnostic procedure in routine services.

The results of the above analyses are presented here in the form of a compilation of papers. Paper 1 presents the results of the first analysis and is now published in the international Journal of Gynaecology and Obstetrics[19]. Paper 2 contains the results of the second analysis and is accepted for publication, but at the time of writing is still *in press,* at *Cadernos de Saúde Pública*[20].

PAPER 1

Title: Attendance for Diagnostic Colposcopy Among High-Risk Human Papillomavirus Positive Women in a Brazilian Feasibility Study

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Keywords: Cervical cancer; Screening; HPV-DNA; Colposcopy; Follow-up; Adherence; Brazil

Synopsis

Colposcopy attendance was limited in a feasibility study of hr-HPV based cervical cancer screening in Sao Paulo, Brazil. Primary care-based colposcopy facilitated access.

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ABSTRACT

Objective

To investigate factors associated with colposcopy attendance in human papillomavirus positive women in Sao Paulo, Brazil.

Methods

We analyzed data from a prospective cohort of high-risk human papillomavirus (hr-HPV) positive women undergoing cervical cancer screening in primary care services in São Paulo, Brazil. Non-pregnant women attending routine screening between Dec 2014 and March 2016 were offered a hr-HPV test, and those testing positive and aged 25 years or older were invited for colposcopy. Sociodemographic information were recorded at study enrollment. We compared variables between women who did and did not attend colposcopy within a logistic regression framework.

Results

Of 1,537 hr-HPV positive women, 1,235 (80.4%) attended for colposcopy, with a median time from primary test to colposcopy of 132 days. Younger age ($p<0.001$) and concurrent negative cytology results ($p=0.025$) were associated with lower attendance. Women registered at units providing both the primary test and colposcopy were more likely to attend than those at units making external referrals (788/862 [91.4%] versus 447/675 [66.2%], $p<0.001$).

Conclusion

Non-attendance for colposcopy may limit the success of future screening programs based on hr-HPV testing in Brazil. Transfer of colposcopy services to primary care is a simple and effective facilitator of attendance.

INTRODUCTION

The global burden of cervical cancer (CC) is shaped by differential access to screening and falls disproportionately on low- and middle-income countries [1]. In Brazil, a middle-income country, the public health system offers a free nationwide CC screening program with Papanicolaou (Pap) cytology and colposcopy directed histological diagnosis followed by treatment [2]. Despite this, only a modest reduction in disease burden has been achieved [3,4] – the annual age-adjusted incidence being 17.1 cases per 100,000 women [5] – with inadequate population coverage with Pap-testing identified as a cause. Younger age, lower socioeconomic status (SES) and poorer access to healthcare are associated with lower rates of Pap-testing in Brazil, and these associations have been unchanged in the last thirty years [6,7]. By contrast, factors influencing adherence to the next diagnostic step – colposcopy amongst women with abnormal Pap results – have scarcely been studied.

Although the current Brazilian screening program is based on conventional cytology, testing for high-risk human papillomavirus (hr-HPV), the causal agent of CC, offers important advantages [8]. Interim Brazilian guidance has cautioned against implementing this technology before existing issues of population coverage and follow-up are addressed [9].

Indeed, if women identified as hr-HPV positive do not attend for colposcopy, this approach would be undermined. This is especially relevant given the current level of knowledge about HPV in the target population [10]. As such, two questions need to be addressed: what individual-level characteristics predict lower colposcopy attendance amongst hr-HPV positive women, and what is the optimal organization of screening services to minimize barriers to colposcopy.

We have previously reported results of the first large-scale feasibility study of liquid based cytology (LBC) and hr-HPV screening in Brazil [11]. The study was conducted in primary care units located in the western and southern districts of Sao Paulo city. The aim of the current analysis was to quantify the rate of non-attendance to colposcopy amongst hr-HPV-positive women, and to identify factors that influence this behavior.

MATERIALS AND METHODS

Detailed methods of the original feasibility study have been described elsewhere [11]. Non-pregnant women registered at primary care units (PCU) in Sao Paulo, and presenting for routine CC screening, were invited to participate. Liquid-Base cytology samples were collected (BD SurePath ™) and sent to the Fundação Oncocentro de São Paulo (FOSP) reference laboratory for hr-HPV testing (BD OnclarityTM HPV Assay) and slide preparation. Cytology was reported according to the Brazilian cytology classification, similar to the Bethesda system [12]. Women aged 25 years or older with a positive hr-HPV test were referred for colposcopy irrespective of the cytology result; women with a negative HPV test but a positive cytology result were managed in accordance with the Brazilian CC screening guideline [2]. Whereby, depending on the cytology class, colposcopy or a repeated cytology is indicated.

Participating health centers were located in the southern and western districts of the city of São Paulo: six PCUs in the west and the Interlagos hospital in the south. The areas served by these units are located in the urban periphery, are socioeconomically deprived and encompass regions of informal housing or *favelas.* Because of the territorial organization of primary care in Brazil [13], with each PCU serving a local area, all participating women who presented to the PCUs for screening were living in the immediate surrounding neighborhoods: Jardim Boa Vista, Jardim D'Abril, Jardim São Jorge, Paulo VI, Vila Dalva Guiherme, and Vila Sônia. The Interlagos hospital serves a larger area, with greater geographic dispersal of the women screened.

Colposcopy services were provided in-house at the Interlagos hospital and the PCU Vila Sônia. Women screened at the Interlagos center who required colposcopy follow-up were offered appointments at the same center; those that screened positive at the PCUs were offered appointments at Vila Sônia, with a limited additional colposcopy service provided at a nearby hospital (Hospital Universitário).

Women who did not attend for colposcopy after the normal processes within their PCU were issued a reminder letter, inviting them for colposcopy, and a phone call. These reminders were provided by the study investigators and were in addition to the routine reminder/recall procedures.

The cytology request form used in routine practice contains fields for age, address, education level and ethnicity. The latter two variables were inconsistently filled in, resulting in limited individual-level sociodemographic information. As such, we aimed to obtain a marker of socioeconomic status (SES) using the participating women's home addresses. The index of social vulnerability in São Paulo state 2010 (IPVS 2010 – Portuguese abbreviation) is a synthetic indicator of deprivation calculated at the level of the census tracts. It was originally designed as a tool to identify areas for government investment [14], but has subsequently been used in a number of studies of different health outcomes [15]. The IPVS-2010 is a composite of parameters measuring household income and family structure, categorizing census tracts into six categories ("very low vulnerability" to "very high vulnerability"), with lower income and younger family structures equating to higher vulnerability categories. We further grouped the two lowest vulnerability categories as "low", the two highest as "high", and the intermediate two categories as "medium" vulnerability. We geocoded participating women's addresses and performed a spatial join with a shape file of census tracts in the Sao

Paulo region. As such, IPVS-2010 categories were assigned to each participant as a proxy for socioeconomic status. Women with missing addresses or living in uncategorized census tracts were excluded from analyses of IPVS-2010.

Analyses were restricted to women aged 25 years and older with a positive hr-HPV test result. This subgroup was chosen because all women had an unambiguous indication for colposcopy within the study protocol; this is different from women with only positive cytology where a repeated cytology may be recommended before colposcopy in accordance with the national guidelines. Age was classified in the following groups: 25-34, 35-44, 45-54, >55 years of age. Cytology class was divided into LSIL and less severe and HSIL, this being the cytology threshold for colposcopy referral in Brazil.

Attendance for colposcopy was calculated as a binary variable: women with a recorded colposcopy result were considered to have attended, and those without to not have. The number of cases of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) that went undetected due to non-attendance was estimated. The CIN2+ detection rates, according to hr-HPV type – assuming that in multiple infections the rate was determined by highest risk type, with 16 > 18 > others – were calculated in women with colposcopy results. These rates were then applied to women who did not attend for colposcopy, according to their hr-HPV type.

The univariate associations between independent variables and attendance were tested with the Chi-squared. A logistic regression model was built to assess the effect of in-house colposcopy on attendance after adjustment for potential confounding variables, with results presented as Odds Ratios and 95% confidence intervals. Variables were included in the model if they altered the association between in-house colposcopy and attendance by >5%.

The time from LBC-sample collection to colposcopy was calculated. Comparison across categorical exposure variables was made using a log-rank test. Analyses were conducted in QGIS3 and Stata 14.1. $P<0.05$ was considered statistically significant.

The Ethics Committee of the Universidade de São Paulo, Faculty of Medicine (FMUSP), approved this study (No. 075/13). Written informed consent was obtained from participants prior to study enrolment.

RESULTS

Between Dec 2014 and March 2016, 16,102 women joined the study; the period of follow-up for colposcopy results was concluded in March 2017. A total of 1,537 women, aged 25 years and older and with a positive hr-HPV result, were included in this analysis. 113 (7.4%) women also had a cytology result of HSIL. The median age was 37 with a range of 25 to 88 years.

1,235 women attended for colposcopy resulting in a global attendance rate of 80.4%. Only 9 (0.7%) colposcopies were performed in private institutions outside of the study sites. The median time from LBC collection to colposcopy was 132 days (Figure 1). Among those women who attended for colposcopy 67 CIN2+ lesions were diagnosed. Projecting the observed CIN2+ rates according to hr-HPV type, we estimated that 17 CIN2+ cases were missed due to non-attendance for colposcopy.

Table 1 presents the individual-level characteristics of the hr-HPV positive women grouped according to attendance for colposcopy. Younger age was associated with lower colposcopy attendance, as was a negative cytology result. There was a similar distribution of education-level and IPVS-2010 categories between women who attended colposcopy and those who did not. Although there were missing data (381 [24.8%] for education and 113 [7.4%] for IPVS-2010) the proportion of missing values was similar between attending and non-attending women.

Attendance rates differed significantly between units providing in-house colposcopy and those referring externally (788/862 [91.4%] versus 447/675 [66.2%], $p<0.001$). The

unadjusted odds ratio (OR) for attendance associated with in-house colposcopy was 5.43 (95% CI 4.10 to 7.27, $p < 0.001$). The OR adjusted for age, IPVS-2010 and cytology status was 5.14 (95% CI 3.81 to 7.01, $p < 0.001$). The median time from LBC-sample collection to colposcopy was 220 days when external referral was required, compared to 102 days where in-house colposcopy was available. Figure 1 presents the time-to-colposcopy data for in-house vs external colposcopy services (log-rank test $p < 0.001$).

DISCUSSION

In the first large-scale feasibility study of CC screening using hr-HPV testing in Brazil, the rate of non-attendance for colposcopy, following a positive test result, was 19.6%. This resulted in an estimated 17 cases of CIN2+ that went undetected, and thus untreated. The provision of an in-house colposcopy service, at the same location as the primary screening test, was associated with greater attendance. In-house colposcopy remained a facilitator of attendance after adjustment for the age, SES and the cytology result.

Our results were obtained within existing primary care services. However, the rate of colposcopy attendance in this study likely overestimates what would be achieved in true routine practice: reminder letters, phone calls and administrative support were provided as part of the study. Even with these bolstered resources, the median time to colposcopy was 132 days. This time included the processing of samples before results were released to the health centers. Previously, "screen-detected" CC has been defined as those diagnosed within four months of cytology [16]. 556 (45.0%) of the participants had a colposcopy within this time frame. These results suggest that non-attendance for colposcopy would be a problem in an hr-HPV testing scenario and limit the effectiveness of this approach within current screening structures.

In this context, it is essential to identify system-level factors that facilitate attendance. Notably, units providing in-house colposcopy achieved a 25.2% greater total attendance than those referring externally. Judged against the four-month standard, 496 (62.9%) women had accessed in-house colposcopy in this time frame, compared to only 90 (20.1%) women being referred externally. Because women live close to the PCUs where the primary tests were

collected, when colposcopy was provided in-house, the distance and transport expenditure to the colposcopy appointment were less. Furthermore, women were likely to be familiar with the environment and health care professionals at their PCU and may have felt more comfortable undergoing colposcopy in this setting.

The odds of colposcopy attendance increased with older age and this association remained after adjustment for other variables. Although malignant cervical disease is uncommon among women in the youngest screen-eligible age group, this group appears to be at risk for non-attendance for subsequent colposcopy and may warrant closer follow-up. Furthermore, the presence of a concurrent positive cytology result was also associated with higher colposcopy attendance. This may reflect a greater familiarity with the smear test – both amongst women and health professionals – with greater salience given to these results. In addition, these women had two abnormal test results as opposed to just one, and this may have resulted in greater motivation to attend colposcopy.

An unexpected finding was the lack of association between education or IPVS-2010 and attendance for colposcopy. In other contexts (for example the United Kingdom [17]) deprivation has been strongly associated with lower colposcopy attendance. We propose two explanations for our results. Firstly, the population being studied – women accessing primary health care within the Brazilian family health strategy – does not cover the entire socioeconomic spectrum but are predominantly women with lower income, poorer living conditions and with access to fewer education opportunities. It is possible, therefore, that no association between SES and colposcopy attendance was found because the population being studied is relatively homogenous with respect to SES. Secondly, although the IPVS-2010 in the census tract of residence is a valid maker of SES, the quality of information is clearly not

equal to an individual-level marker. This kind of measurement error would be expected to bias the estimate towards no association.

In the multivariate analysis, after adjustment for age, cytology result and SES, in-house colposcopy remained strongly associated with greater attendance (OR 5.0, 95% CI 3.7 - 6.7). Therefore, the greater attendance observed in women accessing in-house colposcopy was not accounted for by differences in these potential confounding variables. These findings are in line with other studies where practical barriers to attending colposcopy appointments – including distance, travel costs, work absence, and child-care issues – were identified in different contexts [18,19]. The results of this study show the importance of commissioning colposcopy services locally, within primary care, where the bulk of the initial screening tests is performed.

This work has some limitations. As mentioned above, due to missing individual-level data, a proxy for SES was obtained based on place of residence. Although this approach is widely used (for example in [20]) the results are less reliable than individual-level information. Next, the results may not be generalizable to other parts of Brazil with substantially different socioeconomic and geographic characteristics, and evidence from other regions is needed.

Due to the observational nature of this study, it is not clear if the greater attendance achieved at centers with in-house colposcopy was due to the provision of the service itself or due to other unmeasured factors. Furthermore, current guidelines for hr-HPV primary testing recommend direct referral of HPV16 and HPV18 positive women with an additional triage step for other hr-HPV types [9,21,22]; however, in this study, all hr-HPV women were referred for colposcopy, without further triage. In this respect the results do not accurately

reflect the situation if hr-HPV testing were to be adopted. It is possible that if direct referral had been reserved for HPV16- and HPV-18-positive women, then more resources could have been focused on facilitating their attendance.

Finally, although a key advantage of HPV-based CC screening is the possibility of self-collection [23] – avoiding unnecessary pelvic examinations and facilitating access for women who might otherwise not undergo screening – we were not able to incorporate this strategy in our study. We do however note promising results using self-collection in Brazil, both in existing primary care structures [24] and in remote areas of the Amazon [25].

Non-attendance for colposcopy following a positive hr-HPV test would limit the success of a screening program based on hr-HPV testing in Brazil. It is important to consider innovations to the existing screening system that may improve this metric. Indeed, the results of the study provide initial support for the provision of local, primary care based, colposcopy services. Furthermore, our results support the notion suggested by others [21] that a transition to hr-HPV-based screening should be accompanied by a shift towards an organized, as opposed to opportunistic, screening program in Brazil. However, given the limitations of this work, further research is required to identify system-level facilitators of attendance for colposcopy in Brazil and to evaluate the cost-benefit of any possible innovations to current screening practices, such as transfer of colposcopy to primary care.

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CONFLICTS OF INTEREST

Luisa Villa reports grants and personal fees from Merck, Sharp & Dohme, outside the submitted work, and is occasionally a consultant for companies that develop and sell HPV

tests. José Eduardo Levi reports personal fees from ROCHE, personal fees from QIAGEN, non-financial support from GREINER, during the conduct of the study. José Eluf-Neto reports that BD provided equipment and reagents for this study at no charge. BD had no role in the study design, data analysis or writing of the manuscript. The other authors declare no conflicts of interest.

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Table 1 Individual-level characteristics of hr-HPV positive women according to attendance (or not) to colposcopy, São Paulo, Brazil (2014-2017)

Participant characteristics	Colposcopy		p-value
	Attended n (%)	**Did not attend** n (%)	
Age group (years)			
25-34	508 (74.9)	170 (25.1)	
35-44	318 (80.3)	78 (19.7)	
45-54	215 (86.3)	34 (13.7)	
≥ 55	194 (90.7)	20 (9.3)	<0.001
Level of education Ψ			
Lower than secondary school	470 (82.0)	103 (18.0)	
Secondary school or higher	464 (79.6)	119 (20.4)	0.328
Index of social vulnerability ϕ			
Low	443 (82.2)	96 (17.8)	
Medium	477 (79.4)	124 (20.6)	
High	229 (79.8)	58 (20.2)	0.457
Cytology result			
≤ LSIL	1135 (79.7)	289 (20.3)	
HSIL	100 (88.5)	13 (11.5)	0.025

Ψ missing values: 301 in attended group and 80 in did not attend group; **ϕ** missing values: 86 in attended group and 24 in did not attend group.

Table 2 Results of uni- and multivariable logistic regressions with attendance for colposcopy as the dependent variable

	Unadjusted OR (95% CI)	**p-value**	**Adjusted* OR (95% CI)**	**p-value**
Age (years)				
25 – 35	1.0		1.0	
35 – 44	1.36 (1.01 – 1.85)	0.041	1.40 (1.01 – 1.96)	0.048
45 – 54	2.12 (1.43 – 3.20)	<0.001	2.06 (1.32 – 3.32)	0.002
55+	3.25 (2.03 – 5.46)	<0.001	2.32 (1.40 – 4.03)	0.002
IPVS-2010 category				
Low				
Medium	1.0		1.0	
High	0.84 (0.62– 1.12)	0.228	0.95 (0.69 – 1.30)	0.726
	0.86 (0.60 – 1.23)	0.400	0.86 (0.59 – 1.28)	0.462
Cytology result (HSIL)	1.96 (1.12 – 3.71)	0.026	2.16 (1.16 – 4.43)	0.023
Provision of in-house colposcopy	5.43 (4.10 – 7.27)	<0.001	5.14 (3.81– 7.01)	<0.001

* All variables were included in the model

FIGURE LEGEND

Figure 1: Proportion of women attending for colposcopy over one year of follow up according to provision of in-house colposcopy services, São Paulo, Brazil (2014-2017)

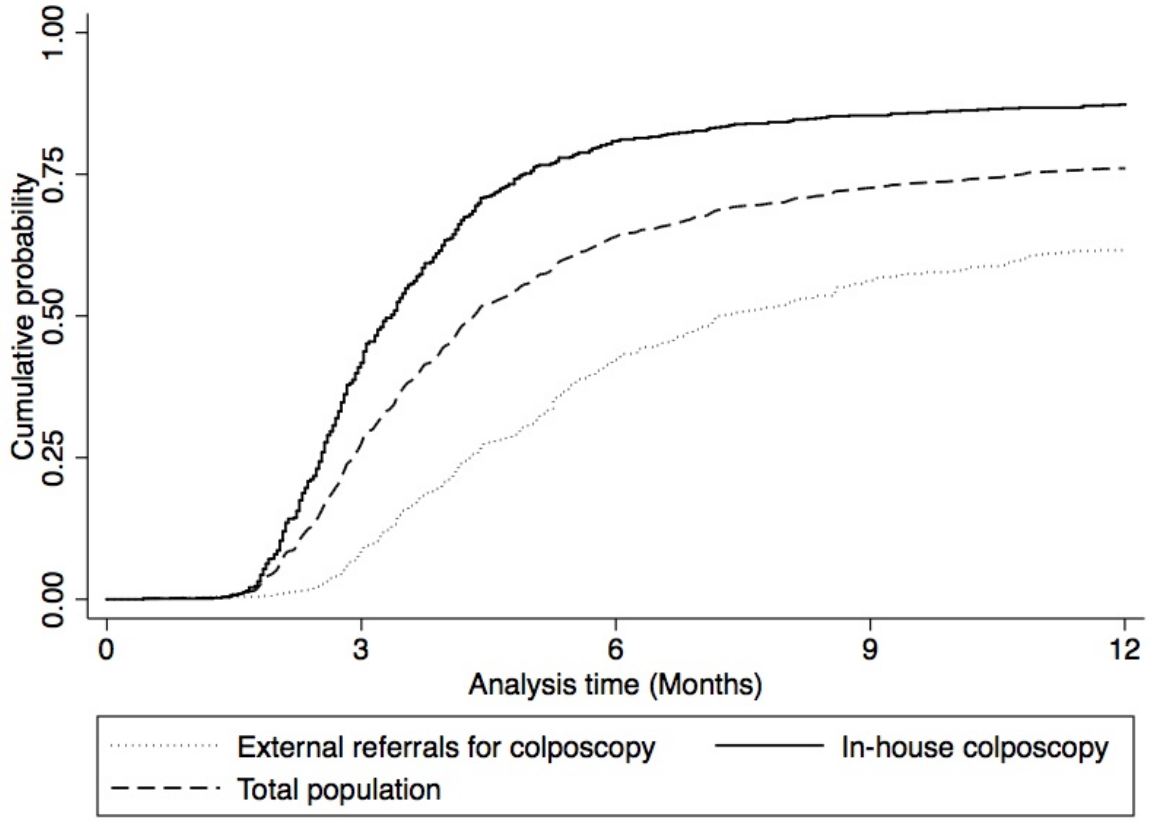
Cumulative probability
0.00
0.25
0.50
0.75
1.00
0
3
6
9
12
Analysis time (Months)
External referrals for colposcopy
In-house colposcopy
Total population

Figure 1

PAPER 2

Title: Access to Colposcopy in the State of Sao Paulo, Brazil: Probabilistic Linkage Study of Administrative Data

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Abstract

Cervical cancer screening is a multistage process. Access to both the primary test and subsequent diagnostic procedures is essential. Considering women undergoing screening on the public health system in the state of São Paulo, we aimed to estimate the proportion of women accessing colposcopy within six months of an abnormal smear result. We retrieved records from two administrative databases: the SISCOLO that contains smear results and the SIA-SUS that records colposcopies. A reference cohort consisted of women, aged 25 years or older, found to have an abnormal smear result between 1st May 2014 and 30th June 2014. We excluded prevalent cases. We linked the reference cohort and records in the SIA-SUS extending to 31st Dec 2014. After excluding prevalent cases, 1761 women with abnormal cytology results were left. 700 (39.8%) linked to a colposcopy record within the follow-up period; this fell to 671 (38.1%) when follow-up was censored at six months. Slightly higher attendance was seen in women living in the metropolitan region of greater São Paulo compared to residents of the rest of the state. There was no association between colposcopy attendance and age or cytology class. These results highlight that access to colposcopy on the public health system in São Paulo is limited. This compromises the quality of screening and the issue needs to be prioritized in service planning.

Introduction

The burden of cervical cancer (CC) is largely shaped by differential access to screening [1]. In Brazil, the public health system (SUS – Portuguese abbreviation) offers free screening with the Papanicolaou (Pap) smear [2]. Access to this test has expanded substantially, and in some state capitals over 80% of the target population is covered [3–5]. However, CC incidence in Brazil remains high compared to some countries with equivalent coverage [1,6].

One explanation for this finding may be limited access to diagnosis and treatment after an abnormal smear result. Women with cytology results suggestive of a high-grade lesion should be directly referred to colposcopy [2]. If a bottleneck exists at the transition from the primary screening test to colposcopy, it would represent an important priority for service planning.

We addressed this question by following a cohort of women with abnormal smear results collected during routine screening in the state of São Paulo, Brazil. We used a probabilistic technique to link the cytology results, recorded in the national CC screening database (SISCOLO) [7], to colposcopy records in a billing database for outpatient procedures (SIA-SUS) [7]. This study is part of a wider project investigating inequalities in access to screening services in Brazil [8–10].

Methods

Data sources

The SISCOLO is a database for monitoring cervical cancer screening activities. The results of smears performed on the SUS are recorded, as well as the date of reporting. Patient identifiers in the SISCOLO are the woman's name, mother's name, date of birth, address and Cartão Nacional de Saúde (CNS) number. The CNS is a unique patient identifier. Unfortunately, its utility in this regard is limited, as some patients have more than one CNS [11]. Furthermore, it is not an obligatory field in the SISCOLO, with only a roughly 50% completion rate.

The SIA-SUS is an administrative billing database for outpatient procedures. As of March 2014, colposcopy services were required to record individual patient information on this system (Portaria No 189, 31 de Janeiro de 2014). Each colposcopy record contains the date and location of the procedure, patient's name, date of birth, address and CNS (obligatory in the SIA-SUS). As such, it serves as a record of the occurrence of a procedure, but without clinical specifics.

Selection of the reference cohort

We identified a cohort of women with abnormal cytology results, that – according to the Brazilian guidelines [2] – required a colposcopy referral. From the SISCOLO we retrieved all records of women aged 25 years and older, resident in the state of São Paulo, and with a cytology class more severe than LSIL. Only women whose results were released between 1st May 2014 and 30th June 2014 were included. This group of women with abnormal cytologies will be referred to as the reference cohort.

Timing considerations and prevalent cases

Not all abnormal results in the SISCOLO represent screening smears. A repeat smear is indicated after a colposcopy when the findings were discordant with the original smear, or when the endocervical canal is not visualized. In addition, six-monthly smears are recommended for follow-up after treatment of a lesion. We sought to exclude these non-

screening smears from the reference cohort, as they represent women already within the colposcopy services.

Given that the SISCOLO does not contain the indication for smears, two procedures were applied to best exclude the prevalent cases. Firstly, we aimed to remove all women in the reference cohort who had received at least one other abnormal result in the preceding 16 months. To achieve this, records in the reference cohort were linked with all abnormal smear results in the SISCOLO between 1st Jan 2013 and 30th April 2014.

Secondly, we reasoned that women undergoing follow-up (concurrent colposcopy and smear) after a treatment in the preceding year, may not be excluded by this procedure. The SISCOLO contains the date the smear result was released, whereas the SIA-SUS records the date the colposcopy was performed. Therefore, these cases would appear as linked records where the colposcopy date preceded the smear date. The reference cohort was linked with the two preceding months in the SIA-SUS (March and April 2014); we excluded all records that linked with a colposcopy before the smear was released. See figure 1.

Finally, to determine the rate of colposcopy attendance, we included records in the SIA-SUS between 1st May and 31st December 2014. This allowed a period of six to eight months in order for a colposcopy to be recorded.

Data manipulation procedures

Cleaning and de-duplication

Data pre-processing and cleaning routines were conducted to minimize differences in typing and to standardize entries between the SISCOLO and SIA-SUS. For the women´s names, accents, double spaces and punctuation were removed. Letters were converted to uppercase and known abbreviations replaced with full names (e.g. Ap -> Aparecida). All prepositions (e.g. “de”, “dos” etc.) were removed and full names were split into first, middle (when more than one only the first was retained), and last names. Name fields were searched for strings consistent with missing values (e.g. “ignorado” and synonyms) as well other (more esoteric) entries that would not be consistent with names. The date of birth was split into separate fields for day, month and year.

The woman's name was completely recorded in the SISCOLO and missing in five records in the SIA-SUS. Mother's name, although not used in the linkage procedure, was far less reliably filled. Date of birth was recorded in 100% of cases in both databases. The CNS was 98% and 58% completed in the SIA-SUS and SISCOLO, respectively. When present, the CNS was used as a key for de-duplication. Given the high level of missing CNS in the SISCOLO and issues with its performance as a unique identifier, the remaining records were then de-duplicated based on exact agreement on name, date of birth, municipality of residence (IBGE code) and mother´s name (in the SISCOLO). Only the first record (date of cytology or date of colposcopy) was retained.

Linkage

Firstly, we made a gold standard dataset of certain (or at least highly probable) matches between the SISCOLO and SIA-SUS, by performing a deterministic linkage between records with a completed CNS. The links were then manually reviewed. 97.4% agreed on name, date of birth and address, or name and either date of birth or address. We used this gold standard dataset to calculate m-probabilities: the probability that a particular field (e.g. first name) agrees given that the two records are truly matched, m = P(agreement | match). The value reflects the data entry error rate; if data entry were error free and completely standardized the m-probability would be 1. Next, we calculated the u-probabilities – the probability that a particular field agrees given that the records are truly unmatched, that is a chance agreement, u = P(agreement | non-match) – from the total set of pairwise comparisons, excluding the known matches [12]. The u-probability reflects the uniqueness, or discriminatory power, of the of the identifier in question.

Complex comparison patterns were generated for agreement on first, middle and last names, using the Jaro-Winkler string comparator [13]. Jaro-Winkler scores range from 0 (perfect dissimilarity) to 1 (perfect similarity) and were divided into five categories, (0,0.75], (0.75, 0.9], (0.9, 0.95], (0.95, 0.99], (0.99, 1). m- and u-probabilities were then frequency adjusted for each category of Jaro-Winkler score [14].

Match weights were calculated according to the Fellegi-Sunter method [15]. That is, for a given pair of records, the match weight was calculated as the sum of the log likelihood ratios determined from the m- and u-probabilities, such that:

$$\text{Log-LR+} = \log_2(m/u)$$
$$\text{Log-LR-} = \log_2((1-m)/(1-u)).$$

Where the Log-LR+ is the positively likelihood ratio use for complete or partial field agreement, and Log-LR- is the negative likelihood ratio used for complete field disagreement.

The calculated match weights had a range of -30 to 24. Following a visual inspection of the distribution of match weights for true and false matches, a cut-off of 15 was chosen, above which matches were included without further review, and below which pairs were rejected. This threshold produced an excellent discriminatory capacity (see sensitivity and specificity below). Serial blocks were used to reduce the total number of comparisons. These were based on combinations of the SoundexBR [16] phonetic code of first, middle and last names; date of birth; and municipality of residence.

The gold standard set was then used to estimate the performance of the linkage strategy. The sensitivity for true matches was 96%. The positive predictive value was found to be 96% and the false positive rate 4%.

Statistical analyses

Age was categorized into four groups as was cytology class. Municipality of residence was classified as those within the metropolitan region of greater Sao Paulo and those living outside this area. The proportion of women with a linked colposcopy record was calculated and categorical variables were compared between these groups using the Chi-squared test.

Women whose cytology results were released at the beginning of the reference period had two months more follow up compared to those with cytology results released at the end of the reference period. In order to account for this, we also calculated the proportion of women that

linked with a colposcopy record within a six-month period from the cytology result being released.

The linkage algorithm was written and implemented in the R language for statistical computing [17]. Specifically functions from the RecordLinakge and SoundexBR packages were adapted for this specific application. The statistical analysis was performed in R version 3.6.3 and Stata 14.1.

Ethics

The project was approved by the University of São Paulo Ethnic Committee CAAE 49655215.0.0000.0065.

Results

We retrieved 2018 abnormal cytology results released between 1st May 2014 and 30th June 2014. Of these 191 linked with an abnormal result in the preceding 16 months and were excluded. Following linkage with the SIA-SUS, a further 66 cases were removing where the colposcopy date preceded the cytology date (see Figure 1). This gave a total of 1761 abnormal cytology records. Of these, 700 (39.8%) linked with a subsequent colposcopy record in the SIA-SUS. There were 671 (38.1%) records that linked with a colposcopy within six months of the cytology result being released.

Table 1 presents the age, area of residence and cytology classes of women in the reference cohort according to linkage status. Cytologies with atypical cells–unable to exclude a high-grade lesion, were over represented amongst women with a linked colposcopy. Women resident in the metropolitan area of greater São Paulo were more likely to have a linked colposcopy record than those living outside of the capital. Figure 2 presents the time from the cytology result to colposcopy as a cumulative probability plot. The figure 2 shows that, among women undergoing colposcopy, the majority occurred within four months of the release of the abnormal cytology result, with few being performed between four and eight months.

Discussion

Among women using the public health system in the State of São Paulo, we found that only 38% of those with abnormal smear results accessed a colposcopy within six months. A higher colposcopy rate was observed for women living in the metropolitan area of greater São Paulo compared to the rest of the state. There was no clear association between rate of colposcopy attendance and women's age or cytology class. These results are based on administrative data (SISCOLO and SIA-SUS). As such, they can be taken to reflect the routine functioning of CC screening services in the state of São Paulo during the period studied.

Colposcopy attendance has previously been estimated in a feasibility study of HPV primary testing in Sao Paulo [18]. In this work, women attending routine screening services were offered a single HPV test. Those with a positive test were invited for colposcopy and 80% ultimately attended. This markedly greater value (80% vs 38% in the present study) has several likely explanations. Firstly, additional administrative support – over and above routine conditions – was provided, with reminder phone calls and letters sent to women that did not attend initially. Secondly, the participating centers were primary care units linked with the University of Sao Paulo, offering a primary care residency program, as well as a hospital specialized in women's health. As such these services are likely to perform above the average. Finally, the period of follow-up was substantially longer than in the present study. Therefore, the present estimate is likely to be more representative of the true situation.

In general, the literature on access to CC screening in Brazil has focused on coverage with the smear test. This line of enquiry has made use of national household surveys [3,4] and aggregate data in the SISCOLO [5]. Population coverage follows a socioeconomic gradient that has been consistent for the last 30 years [19]. In other countries, colposcopy non-attendance has also been associated with greater deprivation [20]. It was not possible to explore this relationship in the present study, as the sociodemographic information recorded in the SISCOLO and SIA-SUS is very limited.

There was, however, a clear divide between attendance in the metropolis (42%) and the rest of the state (34%). A similar rural-urban divide has also been observed in relation to smear coverage [4]. These findings are particularly relevant given the substantially higher mortality from cervical cancer among women living outside the state capitals [21,22]. This may be

explained, in part, by the greater density of health services in these cities. Proximity to screening services has previously been shown to be an important factor influencing access to colposcopy [18].

Previous studies conducted in Brazil have highlighted difficulties in the longitudinal care of women undergoing cervical cancer screening. This is due to a lack of adherence to guidelines on the part of health care professionals, as well as problems in the organization of the health system [23–25]. Our results are similar to those from a study conducted in Goiás state, in which only 35% of women with abnormal cytology results (ASC-H/HSIL) underwent colposcopy [25]. Of note, in this same study, among women with ASC-US/LSIL – in whom the recommended approach is to repeat the smear – 15% were referred for colposcopy unnecessarily.

Studies using aggregate data to estimate the number of colposcopies required at a national level have produced divergent results. Using data from 2015, one study showed that twice the number of colposcopies required were performed in Brazil [26]. This calculation was based on the number of Pap smears performed that year and their known positivity rate [27]. However, using different – and potentially more robust – parameters to estimate the necessity for colposcopies in 2017, a second study found that the number of colposcopies performed nationally was 7% less than required [28].

It is likely that two inter-related problems are co-existing: unnecessary colposcopies in women that do not have an indication and insufficient access to the procedure amongst those that do. This is a doubly problematic situation. It is self-evident that not investigating women with abnormal smears is harmful. However, colposcopy itself is not a benign procedure, carrying the inherent risks of bleeding and infection, and the chance of identifying transient lesions. The US Preventive Task Force (USPSTF) considers colposcopy use to be a proxy for the harms of CC screening [29]. As such, it should be reserved for and targeted towards those that need it.

In Brazil, CC screening is conducted opportunistically, putting the onus on individual women and health care providers. However, there is widespread support for a transition to an organized program [2,30]. Ideally, this would allow resources that are currently used for over

screening to be focused on testing the right women – including at the point of colposcopy referral.

Strengths and limitations

The main strength of this work was the use of administrative databases, meaning that the results reflect the performance of routine screening services and not simply a single unit or trial. Through the use of a gold standard dataset we were able to validate our linkage procedure. Furthermore, we were able to identify only women with an indication based on an abnormal smear result in the SISCOLO, thereby avoiding our results being distorted by inappropriate use of colposcopy.

There are some limitations. Our reference cohort may have been contaminated with prevalent cases – i.e. those already within secondary care services for cervical cancer. It was not possible to definitively exclude all these cases, largely due to limitations of the available data. However, by removing all women with an abnormal cytology in the preceding 16 months, the majority were likely excluded. This is because the primary mode of identification of cases, and therefore entry into secondary screening services, is through an abnormal cytology.

The follow-up period on the SIA-SUS concluded on 31st December 2014. This resulted in six to eight months of follow up depending on the point of entry in the reference cohort. This period was constrained by the original ethical approval for the project. There can be instabilities and seasonal variation in local service provision, and conceivably this could have biased our estimate of access to colposcopy downwards if colposcopy provision in São Paulo state during the study (1st March 2014 to 31st December 2014) were subject to additional pressures. However, to the best of our knowledge the period studied is representative of the typical functioning of colposcopy services in São Paulo state. Furthermore, it is possible that many women in our reference cohort eventually accessed colposcopy after the study follow-up period was completed. However, in other contexts, screen-detected cancers have been defined as those diagnosed within four months of the primary screening test [20]. Our period of follow up substantially exceeded four months, especially considering that entry into the cohort was from the date of result release and not smear collection.

One assumption of our study design was that women accessing primary screening on the public health system did not then undergo a colposcopy in a private service. This assumption is supported by results from a recent feasibility study of HPV-based screening in São Paulo in which less than 1% of women underwent colposcopy in the private sector[18].

Conclusion

In the state of São Paulo, only 38% of women with abnormal smears accessed colposcopy services within six months. Meanwhile, aggregate data suggest that many colposcopies are performed on women without indication. This is wasteful of resources and harmful to both the under- and over-screened women.

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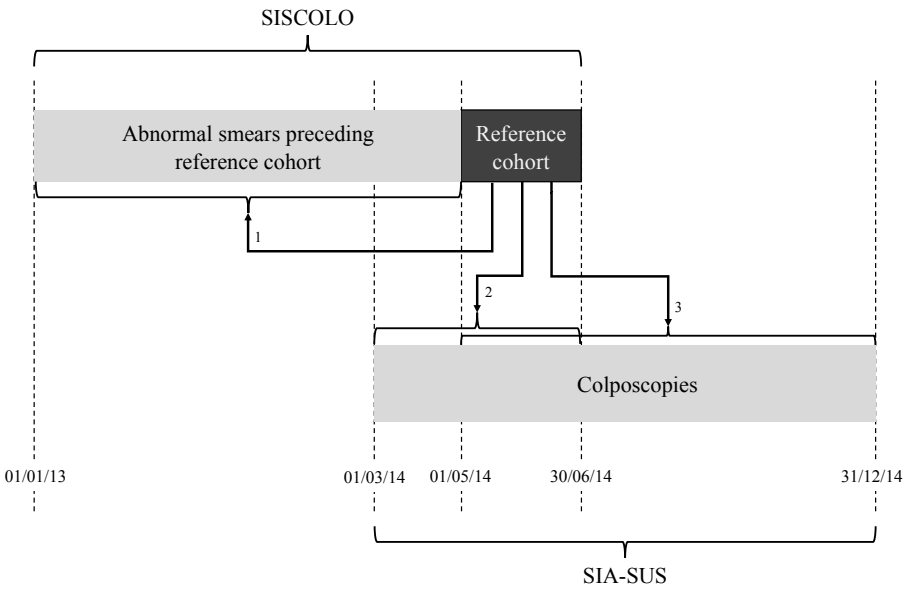
Table 1 Characteristics of women, resident in São Paulo state, with abnormal cytology results recorded on the SISCOLO database between 1st May 2014 and 30th June 2014 – according to linkage status with a colposcopy in the SIA-SUS database

Characteristics of women in reference cohort	**Linked colposcopy records** n = 700 n (%)	**Without linked colposcopy record** n = 1061 n (%)	**p-value**
Age (years)			0.442
25 – 34	208 (29.7)	318 (30.0)	
35 – 44	187 (26.7)	254 (23.9)	
45 – 54	151 (21.6)	258 (24.3)	
55 +	154 (22.0)	231 (21.8)	
Cytology class			<0.001
Atypical cells of undetermined significance (glandular, unknown origin)	147 (21.0)	296 (27.9)	
Atypical cells – possible high-grade lesion (ASC-H, AGUS-H, unknown origin)	356 (50.9)	426 (40.2)	
High grade squamous lesion (HSIL)	187 (26.7)	311 (29.3)	
Invasive cancer (glandular, squamous, unknown origin)	10 (1.4)	28 (2.6)	
Area of residence			0.001
Greater São Paulo	524 (74.9)	719 (67.8)	
Interior of the state	176 (25.1)	342 (32.2)	

Figure Legends

Figure 1 Linkage procedures and formation of the reference cohort. SISCOLO – O Sistema de Informação do Câncer do Colo do Útero (national cervical cancer screening database, containg smear results); SIA-SUS - Sistema de Informações Ambulatoriais de Saúde (outpatient proceedure database containg colposcopy records)

Figure 2 Cumulative probability of linkage with a colposcopy record after the release of an abnormal cytology result – women accessing public screening services in the Brazilian state of São Paulo state in 2014.


SISCOLO
Abnormal smears preceding reference cohort
Reference cohort
1
2
3
Colposcopies
01/01/13
01/03/14
01/05/14
30/06/14
31/12/14
SIA-SUS

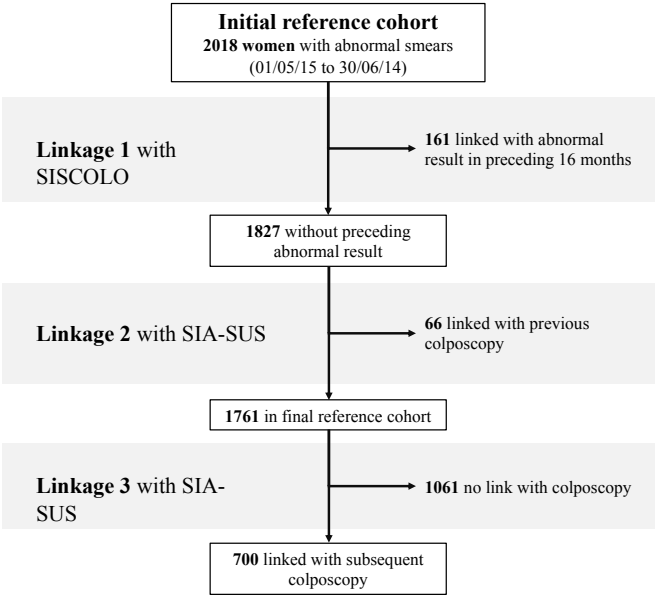

Initial reference cohort
2018 women with abnormal smears (01/05/15 to 30/06/14)
Linkage 1 with SISCOLO
161 linked with abnormal result in preceding 16 months
1827 without preceding abnormal result
Linkage 2 with SIA-SUS
66 linked with previous colposcopy
1761 in final reference cohort
Linkage 3 with SIA-SUS
1061 no link with colposcopy
700 linked with subsequent colposcopy

Figure 1

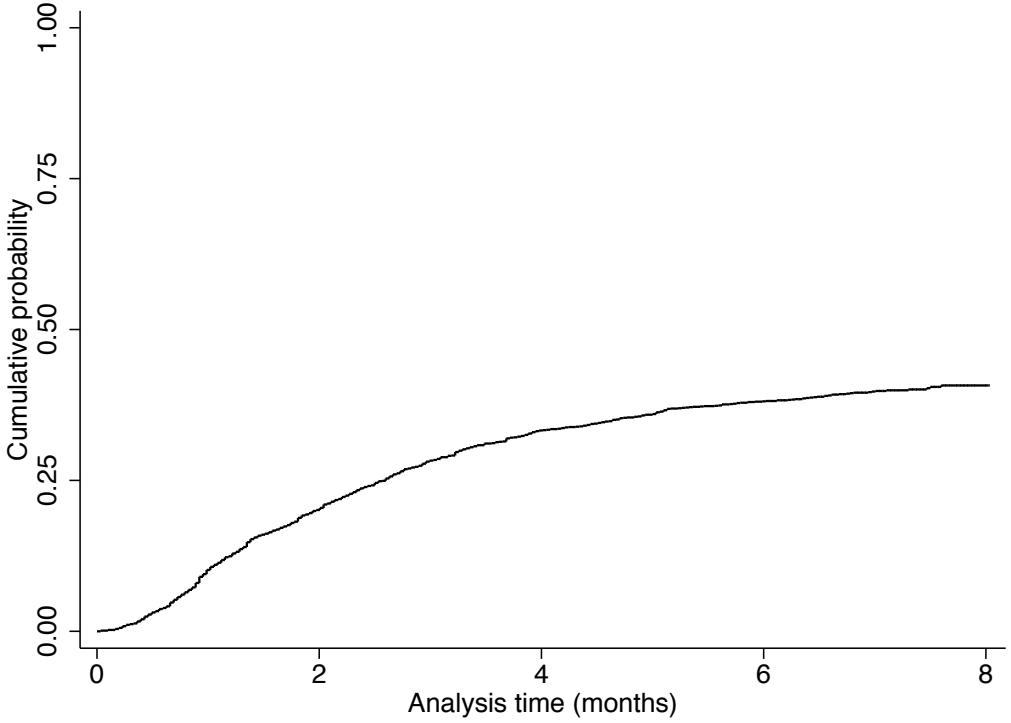

Cumulative probability
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
Analysis time (months)

Figure 2

CRITICAL DISCUSSION

We have presented two complementary data sources that provide insights into the overall integrity of the components of cervical cancer screening, specifically access to colposcopy, in the state of São Paulo, Brazil. We found that among hr-HPV-positive women, participating in a pilot study of hr-HPV testing-based screening, 80% attended for diagnostic colposcopy. Attendance was higher when colposcopy was offered in the same location as the primary screening test. Using administrative datasets, which reflect business-as-usual screening practice, attendance for diagnostic colposcopy among women with abnormal smear tests was found to be lower, only 38% at six months post smear. Taken together, these results suggest that access to colposcopy represents an important bottle-neck within screening services in the state of São Paulo. In this section, we build on the discussions presented in paper 1 and paper 2, to elaborate on a key theme – the co-existence of over and underscreening – and to highlight the most pertinent limitation of these studies in more detail.

Too much, too soon and too little, too late

The concept of too much, too soon and too little, too late was coined in the context of maternal health[21]. Too much, too soon describes the over-medicalization of pregnancy, with early and unnecessary investigation and intervention, that ultimately results in harm. Too little, too late describes the withholding of evidence-based interventions, resulting in harm due to lack of access to appropriate medical services. These problems can, and frequently do, co-exist within the same health systems[21].

Screening is particularly vulnerable to this type of paradox. For example, the evidence-based and well-established periodicity of the Papanicolaou smear, given two previously normal results, is every three years. However, there is widespread misconception, among women and health care professionals, that the smear should be performed annually[22,23]. There is no marginal gain in detection of clinically relevant lesions by increasing the frequency above three-yearly[24], but instead there is significant healthcare system costs, inconvenience and discomfort for the women undergoing the unnecessary smears, and risk of overdiagnosis of transient cervical lesions. At the same time, there is a small but important minority of women that do not access the primary screening test with sufficient frequency to benefit from early

detection. This is the group that would benefit from greater resource allocation and attempts to remove the barriers to access.

The same appears to be true for colposcopy. Our work has shown that access to this procedure is limited among women with a screen-identified cytological lesion. This is expected to result in delayed or missed diagnosis of pre-malignant or early malignant lesions that would be amenable to treatment. Evidence from aggregate data – i.e. the total number of colposcopies performed per region – suggests there is either a surfeit of colposcopies being performed[25], or roughly the appropriate number[26], depending on how the projected requirement for colposcopy is calculated. Taking these two facts together, alongside reports form individual services[27], suggest that many colposcopies are being performed without a valid indication. This is also consistent with the authors' personal observations.

The reasons for this seeming paradox are complex and we were unable to address this theme in the current body of work. It is striking, however, that no single system exists to track the individual components of a joined-up screening system, and a probabilistic linkage was required to identify women across more than one information system. This leads to a lack of oversight and makes individual practice difficult to audit and monitor. This feeds into a broader point about screening system organization, whereby countries that employ opportunistic screening invariably underperform compared to those with nationally organized programs[28]. Proposing changes to the existing system in Brazil is beyond the scope of this work, but it does highlight potential for improvement. The medium-to-long term goal of transitioning to hr-HPV-based screening may be a flashpoint to implement change.

Limitations

A critical limitation of both papers 1 and 2 is the lack of reliable information on socioeconomic status. There is likely to be an interplay between socioeconomic factors and access to downstream screening services, such as colposcopy. It is important to emphasise here that the lack of association between IPVS-2010 in women's census tract of residence and their attendance for colposcopy should be interpreted cautiously. Determining socioeconomic status based on census tract of residence leads to miss-classification bias for three reasons. Firstly, incomplete or inaccurate recording of residential address can result in the incorrect census tract being assigned to an individual. Although this bias was reduced by

manual review of all geocoded addresses, it is impossible to remove this issue completely. Secondly, although location of residence is a proxy for socioeconomic status, it does not necessarily reflect that of the individual themselves, as there can be variation in socioeconomic status within a small geographic region. Finally, the quality of address information is likely to be correlated with socioeconomic status in its own right – i.e. individuals with lower educational attainment are more likely to live in areas of informal housing where addresses are less reliable, and thus be more likely to having a missing datum for IPVS-2010. All three factors would be expected to bias any association with IPVS-2010 and colposcopy attendance towards the null. The analysis of the SISCOLO/SIA-SUS datasets also suffered from a lack of individual-level socioeconomic information. The intersection between these issues could not be characterized adequately in these studies.

CONCLUSIONS

In the above studies, conducted in the state of São Paulo, the rate of colposcopy among hr-HPV-positive women or those with a screen-identified cytological lesion was low. This is likely to lead to delayed or missed diagnoses of treatable lesions. These results highlight a potential area for improvement within existing screening services.

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CSP CADERNOS DE SAÚDE PÚBLICA
REPORTS IN PUBLIC HEALTH

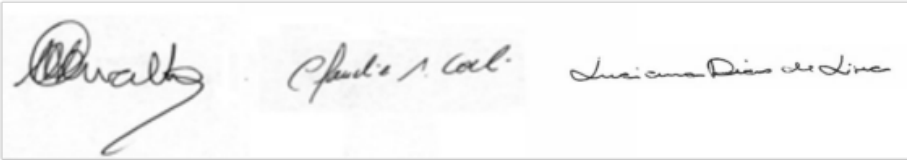
Rio de Janeiro, april 01, 2021.

Dear Dr. Lewis Fletcher Buss:

On behalf of the Editorial Board of Cadernos de Saúde Pública/Reports in Public Health, we are pleased to inform that your article written in collaboration with Lise Cury, CAROLINE MADALENA RIBEIRO, Gulnar Azevedo e Silva, José Eluf Neto, titled "Access to Colposcopy in the State of Sao Paulo, Brazil: Probabilistic Linkage Study of Administrative Data", has been approved for publication on the basis of its scientific merit.

We are currently analyzing your article for possible doubts in relation to formatting and/or bibliographic references and will advise you in due time should they arise.

Sincerely yours,



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PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Citologia líquida e teste molecular para HPV de alto risco: avaliação de novas modalidades de rastreio para prevenção de câncer de colo uterino na Rede Pública de Saúde do Estado de São Paulo

Pesquisador: José Eluf Neto

Área Temática: Área 3. Fármacos, medicamentos, vacinas e testes diagnósticos novos (fases I, II e III) ou não registrados no país (ainda que fase IV), ou quando a pesquisa for referente a seu uso com modalidades, indicações, doses ou vias de administração diferentes daquelas estabelecidas, incluindo seu emprego em combinações.

Versão: 6

CAAE: 08163713.0.0000.0065

Instituição Proponente: Faculdade de Medicina da Universidade de São Paulo

Patrocinador Principal: BECTON DICKINSON INDUSTRIAS CIRURGICAS LTDA
INCT-HPV/Faculdade de Ciências Médicas Santa Casa de Misericórdia de São Paulo

DADOS DO PARECER

Número do Parecer: 3.522.294

Apresentação do Projeto:

Citologia líquida e teste molecular para HPV de alto risco: avaliação de novas modalidades de rastreio para prevenção de câncer de colo uterino na Rede Pública de Saúde do Estado de São Paulo.

Objetivo da Pesquisa:

Em função do atraso na coleta de exames na Região Leste será necessário estender o cronograma até 30/07/2020 e Lewis Fletcher Buss integrará a equipe de pesquisadores auxiliando na tabulação e análise dos dados.

Avaliação dos Riscos e Benefícios:

adequada

Comentários e Considerações sobre a Pesquisa:

adequada

Considerações sobre os Termos de apresentação obrigatória:

adequados

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Recomendações:

aprovar

Conclusões ou Pendências e Lista de Inadequações:

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Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1399777_E3.pdf	19/07/2019 15:42:33		Aceito
Outros	Carta_correcao_inst_coparticipante.pdf	16/05/2018 14:39:19	José Eluf Neto	Aceito
Outros	Carta_resposta_ao_parecer_CEPFMUSP.pdf	23/04/2018 11:37:01	José Eluf Neto	Aceito
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Outros	Solicitacao_extensao_prazo.pdf	23/04/2018 11:33:45	José Eluf Neto	Aceito
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Projeto Detalhado / Brochura Investigador	Projeto Citologia Líquida_corrigido.pdf	15/03/2013 10:55:26		Aceito
Folha de Rosto	Folha de Rosto.pdf	21/02/2013 14:15:09		Aceito
Outros	Parecer FMUSP.pdf	21/02/2013 14:11:18		Aceito

Outros	oficio SES.pdf	22/01/2013 15:58:32		Aceito
Outros	oficios SMS SP.pdf	22/01/2013 15:57:45		Aceito
Outros	Autorização Centro-oeste.pdf	21/01/2013 13:51:46		Aceito
Outros	Termo_Compromisso_pesquisador_SMS.pdf	17/01/2013 10:14:54		Aceito
Outros	Controle_Projeto_SMS.pdf	14/01/2013 16:00:00		Aceito
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Outros	CV Adhemar Longatto Filho.pdf	11/01/2013 15:54:55		Aceito
Outros	CV Luisa Lina Villa.pdf	11/01/2013 15:54:29		Aceito
Outros	CV José Eluf Neto.pdf	11/01/2013 15:51:45		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 21 de Agosto de 2019

Assinado por:
Maria Aparecida Azevedo Koike Folgueira
(Coordenador(a))

Endereço: DOUTOR ARNALDO 251 21º andar sala 36
Bairro: PACAEMBU **CEP:** 01.246-903
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Telefone: (11)3893-4401 **E-mail:** cep.fm@usp.br

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Análise das desigualdades de acesso às ações de controle dos cânceres de mama e do colo do útero no Brasil, com dados dos Estados de São Paulo, Minas Gerais, Bahia e Rio de Janeiro a partir do relacionamento dos sistemas de informações em saúde.

Pesquisador: José Eluf Neto
Área Temática:
Versão: 3
CAAE: 49655215.0.0000.0065
Instituição Proponente: Faculdade de Medicina da Universidade de São Paulo
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.491.274

Apresentação do Projeto:
Submissão de Emenda ao projeto, para registro de inclusão de pesquisador e solicitação de alteração do cronograma

Objetivo da Pesquisa:
Emenda para Inclusão de pesquisador e solicitação de alteração do cronograma

Avaliação dos Riscos e Benefícios:
Sem indicação de alteração

Comentários e Considerações sobre a Pesquisa:
O pesquisador informa "Dificuldades para acesso às bases de dados comprometeu o desenvolvimento do projeto. Considerando-se o volume de informações armazenadas nas bases de dados, bem como a qualidade das mesmas, faz-se necessário estender o cronograma até junho de 2020 e incluir mais um membro na equipe de pesquisadores: Lewis Fletcher Buss.

Considerações sobre os Termos de apresentação obrigatória:
Não se aplica

Recomendações:

Sem recomendações

Conclusões ou Pendências e Lista de Inadequações:

Ciência e Aprovado

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1399771_E2.pdf	19/07/2019 15:48:24		Aceito
Folha de Rosto	Folha_de_rosto.pdf	23/09/2015 14:19:06	José Eluf Neto	Aceito
Outros	Parecer_Fmusp.pdf	23/09/2015 14:16:56	José Eluf Neto	Aceito
Outros	Anexo_II_FMUSP.pdf	23/09/2015 14:14:19	José Eluf Neto	Aceito
Outros	Autorizacao_SES_SP.pdf	21/08/2015 16:02:12	José Eluf Neto	Aceito
Projeto Detalhado / Brochura Investigador	Projeto Desigualdades de acesso ao rastreamento dos cânceres de mama e do colo do útero_Estado de São Paulo e demais.pdf	12/08/2015 11:44:48		Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 07 de Agosto de 2019

Assinado por:

Maria Aparecida Azevedo Koike Folgueira

(Coordenador(a))

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