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CLINICAL ARTICLE

Regional variation in histopathology-specific incidence of invasive cervical cancer among Peruvian women

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ABSTRACT

Objective: To evaluate patterns of cervical cancer incidence in Peru by examining variation in 2 common histopathologic types, squamous cell carcinoma (SCC) and adenocarcinoma (ADC), and analyzing trends over time. *Methods:* Data on the incidence of invasive cervical cancer between 1984 and 2006 were obtained from 3 population-based cancer registries in Peru: Lima, Trujillo, and Arequipa. For each registry, data quality assessment was performed, crude and age-specific incidence was calculated, and time trends were analyzed. *Results:* Overall and SCC incidence varied across registries but incidence of ADC did not. Overall and SCC incidence showed significant declines in Trujillo ($P<0.05$) and modest declines in Lima ($P>0.05$) over time. ADC incidence showed marginally significant increases among women aged 15–29 years in Trujillo ($P=0.10$) and modest increases among young women in Lima ($P>0.05$). *Conclusion:* Population-based cancer registries were an efficient source of data for evaluating the incidence of cervical cancer once data quality had been established. Geographic and temporal variations in cervical cancer burden were documented in Peru. The trends suggest that cervical ADC is increasing among young women in urban Peru, particularly in Trujillo. We recommend supplementing current Papanicolaou test screening with complementary methods of cervical cancer control, including human papillomavirus (HPV) vaccination and HPV DNA testing.

1. Introduction

Cervical cancer is the second most common cancer among women in low-resource countries, where more than 85% of the global burden occurs [1,2]. With the introduction of cervical cancer screening programs based on the Papanicolaou (Pap) test, the incidence of and mortality from cervical cancer have declined worldwide, notably for the most prevalent histopathologic type, squamous cell carcinoma (SCC) [3,4]. However, the opposite trend has been seen for the second most prevalent type, adenocarcinoma (ADC), the incidence of which has increased among young women in high-resource countries [5].

Peru, a middle-income country in South America, has some of the highest incidence and mortality rates of cervical cancer in the world [2,6], but no well-organized cervical cancer screening program. Pap test screening has been sparsely implemented in Peru, especially in rural areas, and suffers from low quality control, insufficient coverage of women at risk, and poor follow-up of women with abnormal results [3]. Additional methods of cervical cancer control are needed; however, the current cervical cancer burden in Peru must be appropriately assessed before recommendations can be made.

We considered that the incidence of cervical SCC and ADC would vary significantly across Peru, demonstrating the heterogeneity of the population. We also considered that the incidence of cervical SCC would show decreasing trends over time, whereas that of cervical ADC would show increasing trends over time, as has been observed in high-resource countries. Evaluating the histopathologic profile of cervical cancer in Peru could influence recommendations for newer methods of cervical cancer control. If the high incidence of SCC remains unchanged in Peru, and/or if the incidence of ADC appears to be increasing, additional methods could be suggested, such as human papillomavirus (HPV) vaccination or high-risk HPV DNA testing [7–10].

The aim of the present study was therefore to evaluate patterns of cervical cancer incidence in Peru by examining regional variations in the 2 most common histopathologic types, SCC and ADC, and by analyzing differences in these patterns over time using data from 3 population-based cancer registries: Lima, Trujillo, and Arequipa.

2. Materials and methods

In a retrospective study, data on the incidence of cervical cancer were retrieved and analyzed from 3 population-based cancer registries covering the largest urban areas of Peru. The Lima Metropolitan Cancer Registry (1990–1998), the Trujillo Cancer Registry (1984–2002), and the Arequipa Population-based Cancer Registry (2004–2006) provided data from the most recent time periods available.

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Peruvian registry directors and the Institutional Review Board at the University of Michigan approved the study proposal.

To verify data quality, assessment of quality was conducted on each registry using only cervical cancer data. Quality indicators were used that were similar to those proposed by the International Agency for Research on Cancer (IARC) in Cancer Incidence in Five Continents Volume IX [6], which included the percentage of cases that were microscopically verified, that were registered from a death certificate only, that had an unknown basis of diagnosis, and for which patient age was unknown [6].

Cases diagnosed as invasive cervical cancer in women aged 15 years and older were included. Tumor morphologies were coded according to the International Classification of Diseases for Oncology, and grouped into one of the following histopathologic types: (1) SCC, 8050–8078, 8083–8084; (2) ADC, 8140–8141, 8190–8211, 8230–8231, 8260–8263, 8310, 8380, 8382–8384, 8440–8490, 8560–8569, 8570–8574, 8576; or (3) other carcinoma (all other specified and unspecified carcinomas). Classification was based on IARC criteria [6], except that adenosquamous carcinoma (8560–8569) was included as ADC. Non-carcinomas and unspecified malignant tumors were excluded from histopathology-specific analyses, but included in overall analyses.

Population data from the 1981, 1993, and 2007 Peruvian censuses were used to estimate the annual female population size for each registry area (Instituto Nacional de Estadística e Informática de Perú). For the inter-census years, linear population growth between censuses was assumed. Comparison of the age distribution of the female population across registry areas showed that the underlying age structure for women aged 15 years and older was similar across registry areas for each census year; therefore, the incidence was not age-standardized.

Statistical analyses were completed by SAS/STAT software version 9 (SAS Institute, Cary, NC, USA). The incidence was calculated for each registry over the appropriate registration time period. The incidence of cervical cancer overall (all cervical cancer cases) and the histopathology-specific incidence of SCC and ADC were calculated and expressed as the number of new cases per 100 000 women per year. The age-specific incidence was also calculated using 15-year age groups: 15–29 years, 30–44 years, 45–59 years, 60–74 years, and ≥75 years. Exact Poisson 95% confidence intervals (CI) were constructed via a macro in SAS/STAT software [11]. The incidence of cervical cancer was then assessed for significant changes over time via linear regression (GLM procedure). The direction of each trend was determined by the β coefficient, and statistical significance was based on an α-level of 0.05. Trend analyses were conducted only for the Lima and Trujillo registries because the Arequipa registry provided too few years of data.

In addition, the proportion of each histopathologic type was calculated by using all cervical carcinomas as the denominator. For each registry, proportions were calculated over the appropriate time period. Significant differences in the proportion of carcinoma type were evaluated between pairs of registries via a χ^2 test ($\alpha = 0.05$). The proportion of carcinoma types by year was also calculated for Lima and Trujillo to investigate trends.

3. Results

With regard to the quality assessment of the cervical cancer data (Table 1), quality indicators for both Lima and Trujillo were within acceptable limits; however, the proportion of cases that were microscopically verified in Arequipa (99.3%) was above the acceptable limit (98.0%). Although the data from Arequipa did not meet all of the international requirements for quality, this registry was included in the analyses owing to the paucity of cervical cancer data available in Peru.

The crude and age-specific incidence of cervical cancer overall is presented with case counts for each registry in Table 2. The overall incidence of cervical cancer of all types differed significantly across registries: Arequipa (47.2 new cases per 100 000 women per year; 95% CI, 43.4–51.2), Trujillo (36.1; 95% CI, 34.5–37.8), Lima (18.9; 95% CI, 18.4–19.3). The age-specific incidence did not differ between Arequipa and Trujillo; however, the incidence was significantly lower in Lima than in Arequipa and Trujillo for the following age groups: 30–44 years, 45–59 years, 60–74 years, and ≥75 years.

The histopathology- and age-specific incidence is also provided, together with case counts, in Table 2. The incidence of SCC was significantly lower in Lima (14.0 new cases per 100 000 women per year; 95% CI, 13.6–14.4) than in Arequipa (29.7; 95% CI, 26.7–33.0) or Trujillo (30.0; 95% CI, 28.6–31.6). The age-specific incidence of SCC showed similar results to the incidence of cervical cancer overall. In contrast, the incidence of ADC did not differ significantly across registries. Only one age group, 45–59 years, had a significantly lower incidence of ADC in Lima than in Trujillo.

Fig. 1 presents time trends in the incidence of cervical cancer across all ages in Lima and Trujillo. Decreasing trends were found in Lima for cervical cancer overall ($\beta = -0.103$, $P = 0.250$) and SCC ($\beta = -0.029$, $P = 0.697$); however, these trends were not significant. In Trujillo, significant decreasing trends were found for cervical cancer overall ($\beta = -0.479$, $P = 0.011$) and SCC ($\beta = -0.345$, $P = 0.024$). In contrast, increasing trends were found for ADC-specific incidence in both Lima ($\beta = 0.051$, $P = 0.349$) and Trujillo ($\beta = 0.050$, $P = 0.239$), but neither trend reached significance.

In Fig. 2, the incidence of cervical cancer over time is shown for Lima and Trujillo according to age group and histopathology. For cervical cancer overall, significant decreasing trends were found in 1 age group in Lima (45–59 years, $\beta = -3.280$, $P = 0.005$) and several age groups in Trujillo (30–44 years, $\beta = -1.684$, $P = 0.005$; 45–59 years, $\beta = -2.963$, $P = 0.012$; 60–74 years, $\beta = -5.038$, $P = 0.001$), with marginally significant declines in the oldest age group in Trujillo (≥75 years, $\beta = -7.839$, $P = 0.067$). Similarly, for SCC, significant decreasing trends were found among age groups in Lima (45–59 years, $\beta = -2.384$, $P = 0.001$) and Trujillo (30–44 years, $\beta = -1.399$, $P = 0.029$; 45–59 years, $\beta = -2.447$, $P = 0.009$; 60–74 years, $\beta = -4.067$, $P = 0.004$), again with marginally significant declines in the oldest age group in Trujillo (≥75 years, $\beta = -4.931$, $P = 0.082$). For ADC, marginally significant increasing trends were found among the youngest age group in Trujillo (15–29 years, $\beta = 0.016$, $P = 0.101$); increasing trends in ADC were also found among younger age groups in Trujillo (30–44 years, $\beta = 0.061$, $P = 0.665$; 45–59 years, $\beta = 0.232$, $P = 0.362$), and among young women in Lima (15–29 years, $\beta = 0.008$, $P = 0.551$; 30–44 years, $\beta = 0.096$, $P = 0.467$); however, these trends did not reach significance.

Table 3 presents the proportions of cervical carcinoma type for each registry. The proportion of SCC was significantly different across registries ($P < 0.0001$); the proportion was highest in Trujillo (89.5%), followed by Lima (82.7%) and Arequipa (72.4%). The proportion of ADC was significantly higher in Lima (12.7%) than in Arequipa (7.9%) or Trujillo (7.8%). Linear regression analyses indicated no significant time trends in the proportion of carcinomas diagnosed as SCC for any registry; however, the proportion of carcinomas diagnosed as ADC increased significantly in Trujillo ($\beta = 0.005$, $P = 0.034$).

4. Discussion

The present study examined geographic and temporal differences in the incidence of histopathology-specific cervical cancer by using data from 3 population-based cancer registries in Peru. Significant heterogeneity was found in the incidence of overall cervical cancer and SCC within Peru, whereas that of ADC was homogeneous. Before the study, we predicted that overall cervical cancer burden would be lowest in Lima, the most economically developed area, and greatest in Trujillo, the least developed area studied; however, the incidence was highest in Arequipa. Given that the Arequipa registry was recently

Table 1
Quality assessment of cervical cancer data in Peru according to registry.

	Registration time period	Population coverage in 2007	Number of cervical cancer cases	Percentage of microscopically verified cases	Percentage of cases with death certificate only	Unknown basis of diagnosis, %	Unknown age, %
Acceptable data range				75–98	≤10	≤10	≤20
Registry							
Lima	1990–1998	4 338 566	6142	90.1	3.1	N/A	0.2
Trujillo	1984–2002	355 202	1837	93.6	3.5	0.2	0.0
Arequipa	2004–2006	413 208	567	99.3[a]	0.5	0.0	0.0

[a] Although the percentage of microscopically verified cases was higher than the acceptable range, data from Arequipa were included in the analyses because of the paucity of cervical cancer data available in Peru.

established in 2002, it may have erroneously included prevalent cases in addition to incident cases, which would overestimate the cervical cancer incidence [12]. Moreover, the observed heterogeneity in incidence may be a result of the disparate time periods analyzed, which should be taken into consideration when interpreting the findings.

There were declines in overall and SCC-specific cervical cancer incidence over time in both Lima and Trujillo; however, significant declines were found only in Trujillo. Although there is no well-organized cervical screening program in either region, the declining rates of SCC might be partly explained by opportunistic screening because cases could be diagnosed earlier as dysplasia rather than invasive cancer [4]. The lack of significant trends in Lima may have been due to the limited number of years of data available for analysis: 9 years of data were available for Lima as compared with 19 years for Trujillo.

Geographic and temporal variations in cervical cancer incidence may reflect population differences or changes in the distribution of cervical cancer risk factors or HPV cofactors. The present results may have been influenced by regional differences or temporal changes in the prevalence of high-risk HPV types, patterns of high-risk sexual behaviors (number of sexual partners and early age at first intercourse), patterns of high-risk reproductive behaviors (high parity and long-term oral contraceptive use), prevalence of co-infection with HIV, prevalence of smoking, frequency of Pap screening, and prevalence of certain sociodemographic characteristics such as poverty and low levels of education [7,13–15]. Given that the study examined 3 comparable urban centers, however, we would expect the above factors to have had a minimal impact on the population differences observed.

There was evidence suggesting a rise in the burden of ADC, particularly among young women in Trujillo. After examining changes in the proportion of cervical carcinoma type, we found that the proportion of ADC increased significantly over time in Trujillo. There were also slight trends toward increasing incidence of ADC in Lima and Trujillo; however, these trends were not significant. When time trends were examined for each age group, we found increasing rates of ADC primarily among young women in both Lima and Trujillo; however, these trends were only marginally significant in Trujillo. Nonetheless, these findings indicate an important development in the evolving cervical cancer burden of Peru.

Similar increases in the burden of ADC have been found among young women in high-resource countries such as the United States and Canada [16,17], in western Europe [18], and more recently in lower-income regions such as Goiânia, Brazil [19]. The rise in ADC

Table 2
Incidence of cervical cancer according to histopathologic type and registry.

	Lima (1990–1998)[a]		Trujillo (1984–2002)[a]		Arequipa (2004–2006)[a]	
	Number of cases	Incidence (95% CI)[b]	Number of cases	Incidence (95% CI)[b]	Number of cases	Incidence (95% CI)[b]
All cases						
Crude incidence	6142	18.9 (18.4–19.3)	1837	36.1 (34.5–37.8)	567	47.2 (43.4–51.2)
Age-specific incidence						
15–29 years	212	2.1 (1.8–2.4)	46	2.9 (2.1–3.8)	10	2.9 (1.4–5.2)
30–44 years	1761	26.0 (24.8–27.2)	500	50.4 (46.1–55.1)	146	54.4 (45.9–64.0)
45–59 years	2205	61.8 (59.3–64.5)	658	119.5 (110.6–129.0)	212	128.3 (111.6–146.8)
60–74 years	1427	77.6 (73.6–81.8)	447	163.4 (148.6–179.3)	140	167.1 (140.5–197.1)
≥75 years	521	76.1 (69.7–82.9)	186	166.9 (143.8–192.7)	59	148.6 (113.2–191.7)
SCC						
Crude incidence	4554	14.0 (13.6–14.4)	1529	30.0 (28.6–31.6)	357	29.7 (26.7–33.0)
Age-specific incidence						
15–29 years	134	1.3 (1.1–1.6)	43	2.7 (1.9–3.6)	6	1.7 (0.6–3.7)
30–44 years	1346	19.9 (18.8–21.0)	430	43.4 (39.4–47.7)	89	33.2 (26.6–40.8)
45–59 years	1674	46.9 (44.7–49.2)	532	96.7 (88.6–105.2)	131	79.3 (66.3–94.1)
60–74 years	1041	56.6 (53.2–60.2)	383	140.0 (126.4–154.8)	92	109.8 (88.5–134.6)
≥75 years	350	51.1 (45.9–56.8)	141	126.5 (106.5–149.2)	39	98.3 (69.9–134.3)
ADC						
Crude incidence	700	2.2 (2.0–2.3)	134	2.6 (2.2–3.1)	39	3.3 (2.3–4.4)
Age-specific incidence						
15–29 years	25	0.2 (0.2–0.4)	1	0.1 (0.0–0.4)	1	0.3 (0.0–1.6)
30–44 years	226	3.3 (2.9–3.8)	44	4.4 (2.2–6.0)	13	4.8 (2.6–8.3)
45–59 years	268	7.5 (6.6–8.5)	61	11.1 (8.5–14.2)	15	9.1 (5.1–15.0)
60–74 years	137	7.5 (6.3–8.8)	18	6.6 (3.0–10.4)	8	9.6 (4.1–18.8)
≥75 years	44	6.4 (4.7–8.6)	10	9.0 (4.0–16.5)	2	5.0 (0.6–18.2)

Abbreviations: ADC, adenocarcinoma; CI, confidence interval; SCC, squamous cell carcinoma.
[a] Registration time period.
[b] The incidence is reported per 100 000 women per year.

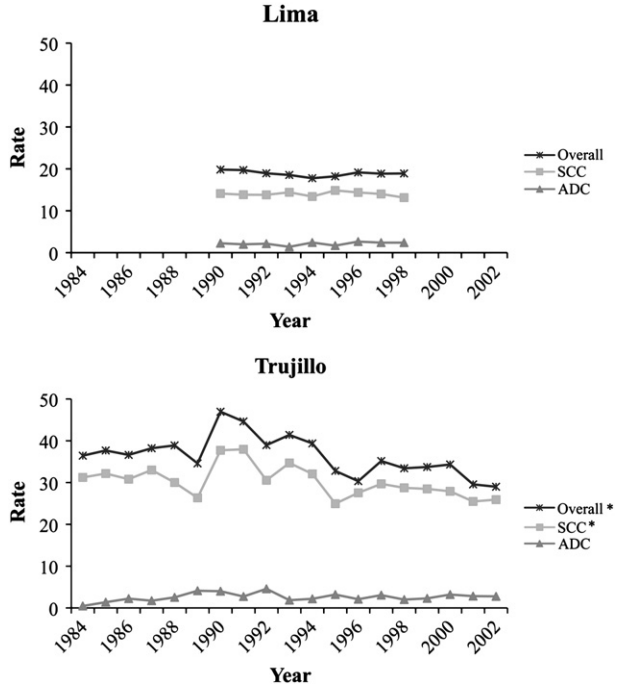

Fig. 1. Trends in the incidence of histopathology-specific cervical cancer according to registry. The incidence is reported per 100 000 women per year. There was a significant decrease in overall and SCC incidence over time in Trujillo (*$P<0.05$). Abbreviations: ADC, adenocarcinoma; SCC, squamous cell carcinoma.

Table 3
Proportion of cervical carcinomas according to histopathologic type and registry.

	Lima (1990–1998)[a]	Trujillo (1984–2002)[a]	Arequipa (2004–2006)[a]	*P* value
SCC	0.827	0.895	0.724	<0.0001 (L vs A) <0.0001 (L vs T) <0.0001 (A vs T)
ADC	0.127	0.078	0.079	<0.05 (L vs A) <0.0001 (L vs T)
Other	0.046	0.027	0.197[f]	<0.0001 (L vs A) <0.05 (L vs T) <0.0001 (A vs T)

Abbreviations: ADC, adenocarcinoma; SCC, squamous cell carcinoma; A, Arequipa; L, Lima; T, Trujillo.
[a] Registration time period.

burden may reflect limitations of cytology-based screening. Pap tests may not adequately detect ADC precursor lesions because these lesions are located higher in the endocervical canal, making them less accessible than SCC lesions for testing [7,20,21]. In addition, Pap test has low sensitivity for the detection of ADC (45%–76%), and produces more false negatives as compared with SCC lesions [20]. The inability to adequately detect ADC precursor lesions ultimately allows invasive ADC to develop without detection, and is a limitation of conventional screening.

One of the strengths of the present study is its novelty. Few studies have been published using cancer registry data from low-resource countries, such as Peru, to describe intra-country variation in cervical cancer incidence and histopathology. Utilizing existing data from population-based cancer registries facilitated a time- and cost-efficient method of describing cancer burden in a population, which is especially beneficial in low- and middle-income countries. However, data quality should be established first.

The results of the data quality assessment showed that cervical cancer data quality was high in Lima and Trujillo; however, Arequipa had a high proportion of cases that were microscopically verified (99.3%). Although a value close to 100% is desirable in high-income countries, it is problematic in low-resource countries, where it typically suggests an over-reliance on pathology laboratories in diagnosing cervical cancer cases, and/or an inability to locate cases diagnosed by other methods [22]. In low-resource countries, the likelihood is greater that cervical cancer cases do not enter the healthcare system; therefore, the identification of cases by other means, such as death certificates, is particularly important. Arequipa was included in the analyses even though the data did not meet international quality requirements; however, data quality should be considered when interpreting the data.

As is the case with all cancer registry data, changes in the number of cases, missing data, and misclassification of histopathology diagnoses are capable of altering the incidence. In terms of population denominators, we assumed that there were no errors in population counts provided by each census and assumed linear population

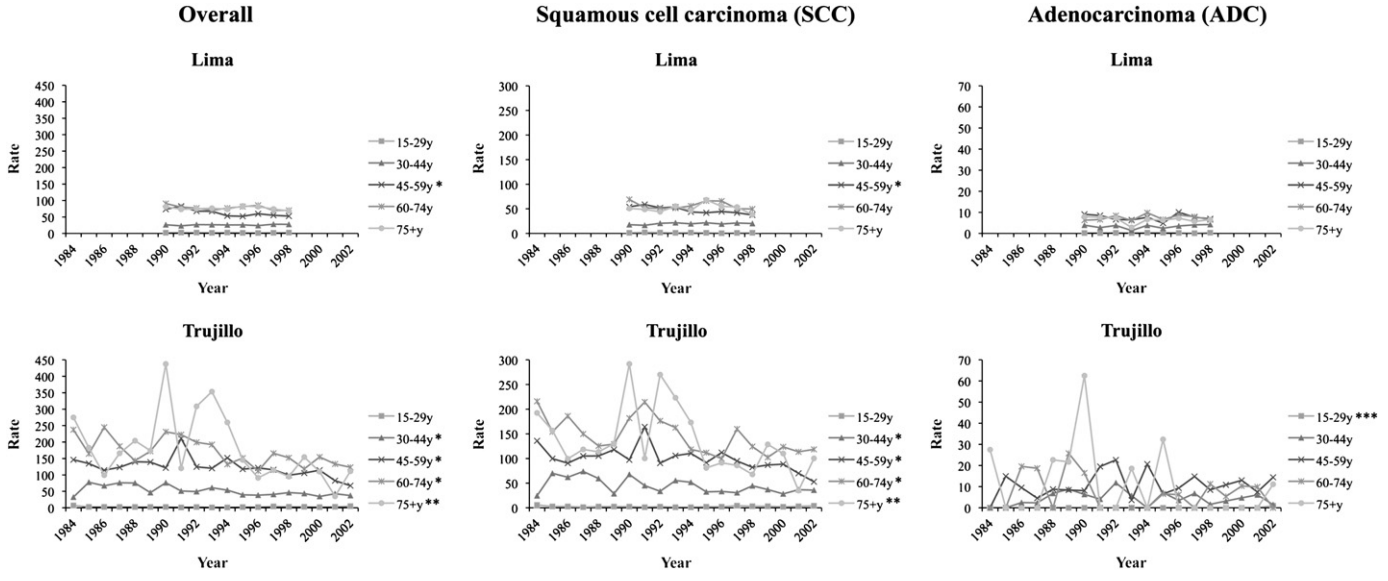

Fig. 2. Trends in cervical cancer incidence according to age group, histopathology, and registry. The incidence is reported per 100 000 women per year. The incidence changed over time as indicated: significant decrease, *$P<0.05$; marginally significant decrease, **$P<0.10$; marginally significant increase, ***$P<0.10$.

growth between censuses. In terms of time trend analyses, we had insufficient data to assess trends in Arequipa, and there was little overlap in registration time periods across registries, which prevented us from making direct comparisons. In addition, even though the Trujillo cancer registry met international data quality requirements, fluctuations were observed in age-specific cervical cancer incidence over time, which may reflect local attempts to introduce cervical screening programs targeting specific age groups. Nevertheless, we believe that the study provides an adequate evaluation of cervical cancer histopathology across the 3 Peruvian cancer registries.

The study showed that histopathology-specific cervical cancer incidence varied both across regions of Peru and over time in certain registries and age groups. There were also trends suggesting an increase in ADC burden among young women, particularly in Trujillo. Population-based cancer registry data proved to be an efficient source for evaluating cervical cancer patterns among Peruvian women once data quality had been established. The results from the study should be used to influence decisions regarding complementary screening methods in Peru. Because ADC may be increasing among young women in urban areas of Peru, we recommend supplementing current Pap test screening with HPV vaccination and HPV DNA testing, which may be more capable of reducing the cervical cancer burden than cytology-based methods alone [7–10].

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Conflict of interest

The authors have no conflicts of interest.

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