

## ARTICLE

# Effect of VIA Screening by Primary Health Workers: Randomized Controlled Study in Mumbai, India

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**Background** Cervical cancer is the leading cause of cancer mortality among women in India. Because Pap smear screening is not feasible in India, we need to develop effective alternatives.

**Methods** A cluster-randomized controlled study was initiated in 1998 in Mumbai, India, to investigate the efficacy of visual inspection with acetic acid (VIA) performed by primary health workers in reducing cervical cancer mortality. Four rounds of cancer education and VIA screening were conducted at 24-month intervals in the screening group, whereas cancer education was offered once at entry to the control group. The study was planned for 16 years to include four screening rounds followed by four monitoring rounds. We present results after 12 years of follow-up. Poisson regression method was used to calculate the rate ratios (RRs); two-sided  $\chi^2$  was used to calculate the probability.

**Results** We recruited 75360 women from 10 clusters in the screening group and 76178 women from 10 comparable clusters in the control group. In the screening group, we achieved 89% participation for screening and 79.4% compliance for diagnosis confirmation. The incidence of invasive cervical cancer was 26.74 per 100 000 (95% confidence interval [CI] = 23.41 to 30.74) in the screening group and 27.49 per 100 000 (95% CI = 23.66 to 32.09) in the control group. Compliance to treatment for invasive cancer was 86.3% in the screening group and 72.3% in the control group. The screening group showed a statistically significant 31% reduction in cervical cancer mortality (RR = 0.69; 95% CI = 0.54 to 0.88;  $P = .003$ ).

**Conclusions** VIA screening by primary health workers statistically significantly reduced cervical cancer mortality. Our study demonstrates the efficacy of an easily implementable strategy that could prevent 22 000 cervical cancer deaths in India and 72 600 deaths in resource-poor countries annually.

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Cervical cancer is the most common cancer among women in most developing countries in Asia, Africa, and Latin America (1). Globally cervical cancer cases increased from 378 000 to 454 000 per year during the period from 1980 to 2010, reflecting a 0.6% annual increase (2). Cervical cancer continues to be the most common cause of cancer death among women in India (3). An estimated 141 768 new cases and 77 096 deaths due to cervical cancer occurred in India in 2010, contributing 26% and 27% to the global cervical cancer incidence and mortality respectively (1). In 1992, the Indian Council of Medical Research determined that Pap smear screening cannot be implemented in India because of lack of infrastructure and trained personnel (4). A Government of India–World Health Organization joint committee constituted in 2006 to develop national guidelines for cervical cancer screening in India also observed that for the large population in India the infrastructure and resources do not permit a Pap smear–based national screening program and

that alternative strategies that are feasible and scientifically valid should be identified (5).

Visual inspection of the cervix after application of 4% acetic acid (VIA) is an alternative low-cost method that has been investigated in recent years. It has been determined that screening women once in a lifetime at the age of 35 years with a one- or two-visit screening strategy involving VIA could reduce the lifetime risk of cervical cancer by approximately 25% to 36% and cost less than 500 US dollars per year of life saved (6). In a critical assessment of screening methods for cervical neoplasia, sensitivity of VIA for detection of cervical precancer and invasive cervical cancer varied from 67% to 79% and specificity varied from 49% to 86% (7). Although the efficacy of VIA screening when performed by trained nurses has been tested in a randomized controlled study in India (8), it would be difficult to assign adequate numbers of trained nurses for a national screening program. In our study, we investigate the feasibility and efficacy of VIA performed by trained

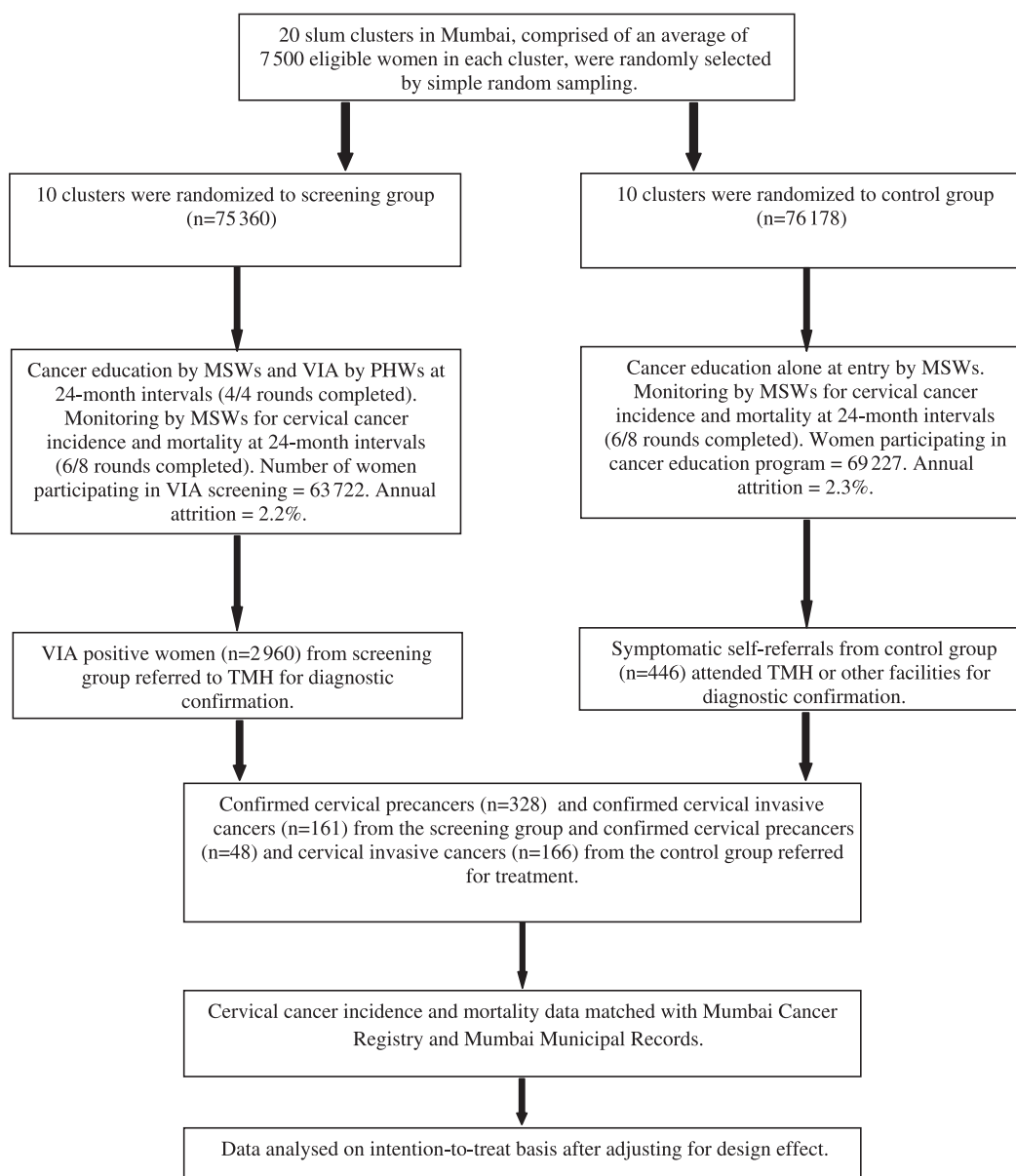
primary health workers (PHWs) in reducing cervical cancer mortality among women aged 35 to 64 years living in Mumbai, India. We present herein the results after 12 years of follow-up.

## Methods

This is a community-based, cluster-randomized controlled study that investigates the efficacy of cancer education provided by trained medical social workers (MSWs) along with VIA screening performed by trained PHWs in reducing cervical cancer mortality among women aged 35 to 64 years. Twenty geographically distinct clusters in Mumbai were selected by simple random sampling from seventy low socioeconomic housing clusters. These clusters, each comprised of an average of 7500 women aged 35 to 64 years, were numbered and randomly assigned to screening or control groups. The screening group received four rounds of cancer education and

VIA at 24-month intervals, whereas the control group received one round of cancer education at the time of recruitment. Both groups were actively monitored at 24-month intervals by MSWs for cervical cancer incidence and mortality. The entire study was planned for a period of 16 years to include four screening rounds followed by four monitoring rounds (Figure 1).

MSWs with previous experience of working in community health programs were recruited and trained for 4 weeks to conduct population surveys, impart cancer education, provide counsel for informed consent, conduct pre- and postscreening counseling, ensure follow-up, facilitate patient navigation, and monitor cancer incidence and mortality in the study areas. PHWs were selected from women who had up to 10th grade education, with prior experience of working in community health programs and good communication skills, preferably living in the selected clusters. They were trained intensively for 4 weeks to perform VIA (per IARC



**Figure 1.** Flow diagram of the trial. MSWs = medical social workers; PHWs = primary health workers; TMH = Tata Memorial Hospital; VIA = visual inspection with acetic acid.

Manual) (9). The PHWs and MSWs received 1-week refresher training annually.

Local government health-care providers and social, political, religious, and other opinion leaders of the community were approached by MSWs and apprised of the goals, potential benefits and harms, and general procedures involved in the study. Their cooperation was invaluable for the smooth and efficient running of the study. To identify eligible women, we used census and electoral lists and conducted a door-to-door survey in the 20 selected clusters. This opportunity was also used for sensitizing the eligible women about the proposed study. Community-based cancer education program using audio-visual media were conducted in the screening and control groups by MSWs. In the screening group, women were additionally invited to attend VIA screening. Women between the ages of 35 to 64 years, living in the selected slum clusters for more than 1 year, and without any previous history of cervical, breast, or any other malignancy were included in the study. Women who attended the screening clinic were once again explained about the aims and objectives of the study, screening techniques, and any side effects that may arise. Women from screening and control groups were additionally provided information about Pap smear screening and the availability of any Pap smear screening facilities in the vicinity, if they wished to screen with Pap smear instead. They were then asked to sign a consent letter written in the local language if they chose to participate in the study. An independent witness from the same community signed the consent letter along with the participant. Thereafter, participants were examined by PHWs in temporary screening clinics specially set up in the study clusters. An expert gynecologist, who was blinded to the observations of the PHWs, independently re-examined 5% of all screened women for purpose of quality assurance.

All women who tested positive on VIA screening (primary screening) were referred to the preventive oncology clinic at Tata Memorial Hospital (TMH), where they received VIA, colposcopy examination by gynecologists, and Pap smears. Women who were clinically positive on colposcopy received directed biopsies. Average time lag between the primary screening and diagnosis was 7 days. Experienced pathologists from TMH reported on the findings. All diagnostic and therapeutic services were provided at no cost. Those with histologically confirmed invasive and preinvasive cancers were given treatment as per the TMH protocols (10).

The control group received the same community rapport-building procedures, baseline surveys, and community-based cancer education as the screening group, except that the women were not invited for screening. All women in the control group were asked to report to TMH in case they detected any symptoms suggestive of cervical cancer. They were also provided free diagnosis and treatment at TMH.

The study protocol was approved by the institutional review board and its progress reviewed and monitored on an annual basis by the institutional review board and an independent data safety monitoring committee. The study is registered with the clinical trials registry of India and ClinicalTrials.gov (NCT00632047; CTR1/2010/091/001205)

## Statistical Methods

Data were collected by door-to-door visits conducted at 24-month intervals by MSWs. The completed questionnaires were physically verified and entered into an electronic database

using a double data entry procedure. Statistical analysis was performed on an intention-to-treat basis using STATA 10 software (StataCorp, 4905 Lakeway Drive, College Station, TX 77845). For calculating incidence rates in both groups, the number of person-years was determined from the date of entry into the study to the date of diagnosis. For mortality rates, the number of person-years was calculated from date of entry to the date of death. Events were considered as censored due to migration, loss to follow-up, and death due to other causes. For all-cause mortality estimation, all deaths in both groups were included. The earliest date of entry was May 15, 1998, and the last date of exit for purpose of analysis was December 31, 2011. Poisson regression model was used to estimate incidence and mortality rate ratios (RRs) and their 95% confidence intervals (CIs). Adjustments were made for design effect. The study was planned to have 80% power at 5% significance level to detect 50% reduction from cervical cancer mortality within 16 years of enrollment. The death rate from cervical cancer was assumed to be eight per 100 000 based on Mumbai Cancer Registry data (11). We estimated that a cluster with an average size of 7500 women will provide approximately 1 115 000 person-years of observation in 16 years. We assumed a coefficient of variation of 0.1. With the effect of intracluster correlation, the true rates of death from cervical cancer would therefore vary between 6.4 per 100 000 and 9.6 per 100 000 in the control group. This leads to a design effect of 1.1. With the selected 10 pairs of matched clusters, we could expect 65 deaths from cervical cancer in the control group. However, the observed mortality rate in the control group was higher than assumed, which enabled us to detect a statistically significant reduction in mortality earlier than planned, at the end of 12 years. All statistical tests were two-sided, and a *P* value less than .05 was considered statistically significant.

## Results

We recruited 75 360 women from 10 clusters in the screening group and 76 178 women from 10 comparable clusters in the control group. A comparison of relevant sociodemographic variables and risk factors between the screening and control groups showed that successful randomization was achieved (Table 1). The screening and control groups had 72.1% and 72.2% women aged less than 50 years, with a median age of 45 years. These figures are similar to the female population structure of India at large (12).

In the screening group, we had 71.5%, 61.5%, 57.8%, and 58.1% participation rates for screening rounds 1, 2, 3, and 4 respectively. Overall 89% of the participants were screened at least once. Compliance rate for diagnosis was 79.4%. Compliance rates for treatment completion were 84.9% and 86.3% for precancers and invasive disease, respectively. We saw an annual average attrition of 2.2% and a cumulative attrition of 21.5% in the screening group. Screening positivity rates increased over time from 1.3% to 2.5%. The interobserver variability coefficient kappa ( $\kappa$ ) between the expert and the PHWs was 0.84.

The control group had a 91% participation rate for cancer education, 88.6% compliance to biennial monitoring, 72.3% compliance with treatment completion, annual average attrition of 2.3%, and cumulative attrition of 22.6%.

**Table 1.** Distribution of sociodemographic variables and risk factors\*

Variables	Screening group (n = 75 360)	Control group (n = 76 178)
Mean age (SD)	44.84 (7.86)	44.92 (8.01)
Mean age at marriage (SD)	17.99 (3.89)	17.85 (3.82)
Mean age at first child birth (SD)	20.82 (3.70)	20.74 (3.61)
Average number of children (SD)	3.58 (1.61)	3.56 (1.61)
Educational status, No. (%)		
Did not attend formal school	29 512 (39.32)	30 797 (40.55)
Primary school	42 198 (56.23)	41 345 (54.44)
≥ High school	3340 (4.45)	3806 (5.01)
Monthly income, No. (%)		
<Rs. 500	35 394 (47.19)	34 472 (45.40)
Rs. 501–1000	34 949 (46.59)	37 156 (48.93)
> Rs. 1000	4667 (6.22)	4307 (5.67)
Occupation, No. (%)		
Housewife	66 490 (88.60)	69 860 (91.93)
White collar	2112 (2.81)	1957 (2.58)
Blue collar	4718 (6.29)	3083 (4.06)
Self-employed	1728 (2.30)	1089 (1.43)
Religion, No. (%)		
Hindu	58 449 (77.89)	60 035 (79.02)
Muslim	9746 (12.99)	8653 (11.39)
Others	6844 (9.12)	7284 (9.59)
Marital status, No. (%)		
Unmarried	295 (0.40)	454 (0.60)
Married	61 582 (82.59)	62 048 (82.62)
Separated	393 (0.53)	302 (0.40)
Widowed	12 289 (16.48)	12 301 (16.38)
Previous consultation for gynecological complaints, No. (%)		
Yes	7816 (10.70)	7298 (9.87)
No	65 212 (89.30)	66 667 (90.13)

\* The total for each variable may not add up to the listed number for each group because of the absence of data with reference to that variable for some participants.

After 12 years of follow-up, we recorded 328 precancers (n = 219 low-grade squamous intraepithelial lesions; n = 19 high-grade squamous intraepithelial lesions) and 161 invasive cervical cancers in the screening group, whereas in the control group, we recorded 48 precancers (n = 35 low-grade squamous intraepithelial lesions; n = 13 high-grade squamous intraepithelial lesions) and 166 invasive cervical cancers (Table 2). The incidence of invasive cervical cancer was 26.74 per 100 000 (95% CI = 23.41 to 30.74) in the screening group and 27.49 per 100 000 (95% CI = 23.66 to 32.09) in the control group. We had observed statistically significant downstaging after three screening rounds (13); we note that downstaging continues to be statistically significant even 12 years after randomization (ie, 4 years after cessation of screening) ( $P = .002$ ) (Table 3). Accurate staging information was not available for 23 case patients from the screening group and 36 case patients from the control group, which is an important limitation of the study.

There were 67 and 98 cervical cancer deaths in the screening and control groups, respectively. This translated into a 31% reduction in cervical cancer mortality in the screening group compared with the control group (mortality RR = 0.69; 95% CI = 0.54 to 0.88;  $P = .003$ ). During this period, the total number of deaths from all causes was 4909 in the screening group and 5275 in the control group (mortality RR = 0.93; 95% CI = 0.79 to 1.10;  $P = .41$ ) (Table 4).

The cumulative incidence and mortality curves (Figures 2 and 3) showed that the incidence and mortality were initially higher in the screening group compared with the control group. The small excess incidence (overdiagnosis) in the screening group disappeared

**Table 2.** Cervical preinvasive case patients\*

Type of lesion	Screening group, No.	Control group, No.
LSIL	219	35
HSIL	109	13
Total	328	48

\* HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.

**Table 3.** Downstaging of cervical cancer\*

Disease stage	Screening group	Control group	Total
<IIB	50	25	75
≥IIB	88	105	193
Total	138	130	268

\* Two-sided Pearson  $\chi^2 = 9.6005$ . Probability = 0.002.

by the seventh year. For mortality, a crossover occurred at 3 years, leading to a statistically significant reduction of 31% in the screening group by the 12th year.

## Discussion

This is the first randomized controlled study that demonstrates that VIA performed by PHWs can lead to a statistically significant

**Table 4.** Incidence and mortality after 12 years (until December 2011)\*

Outcome	Screening group				Control group				P	
	No.	PYO	Crude rate (95% CI)	AAR (95% CI)	No.	PYO	Crude rate (95% CI)	AAR (95% CI)		IRR (95% CI)
Cervical cancer incidence	161	602 152.3	26.74 (23.41 to 30.74)	28.98 (24.51 to 33.45)	166	603 811.8	27.49 (23.66 to 32.09)	29.44 (27.15 to 31.73)	0.973 (0.795 to 1.190)	.79
Cervical cancer mortality	67	602 696.5	11.12 (9.09 to 13.78)	14.44 (12.68 to 16.20)	98	604 228.2	16.22 (14.05 to 18.82)	19.83 (17.83 to 21.83)	0.685 (0.535 to 0.878)	.003
All-cause mortality	4909	602 696.5	814.51 (721.54 to 920.03)	1340.48 (1321.18 to 1359.61)	5275	604 228.2	873.01 (778.08 to 980.08)	1391.25 (1372.09 to 1410.41)	0.933 (0.792 to 1.100)	.41

\* Crude and age-adjusted rates [(AARs; adjusted for world standard population (28,29)] are per 100000 women years of observation. Probability was calculated using two-sided Pearson's  $\chi^2$  test. IRR = incidence rate ratio calculated by Poisson regression model after adjusting for cluster design; PYO = person-years of observation.

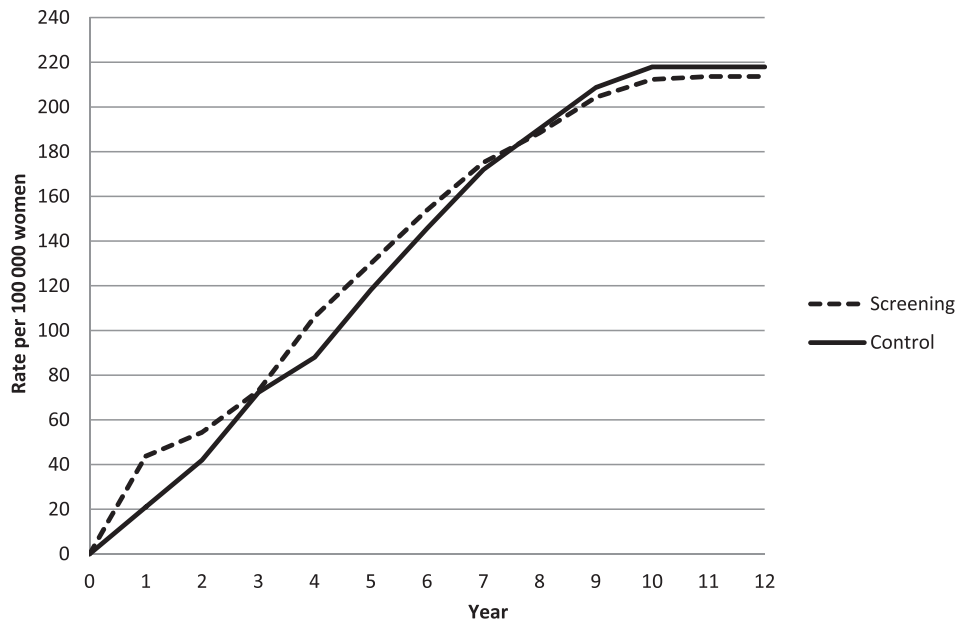
reduction in cervical cancer mortality. It also shows a 7% reduction in mortality from all causes. Our study demonstrates that just 4 weeks of intensive training given to PHWs can equip them to perform cervical cancer screening by VIA effectively, their performance being as good as that of an expert ( $\kappa = 0.84$ ). The fact that the incidence of cervical cancer in the control and screening groups was similar at 12 years suggests that the rate of overdiagnosis, if any, was minimal. This finding contrasts with other screening studies using cytology, which have recorded varying degrees of overdiagnosis (14–18). Our study is the first to document a mortality paradox in cervical cancer screening (excess early deaths in screening group), although this has been well documented in breast, prostate, and lung cancer screening studies (19–23). In our study, VIA detected 328 cases of preinvasive cancers in the screening group compared with 48 cases in the control group. This finding and the fact that we had around 84.9% compliance to treatment among the detected precancers suggests that incidence of cervical cancer in the screened group will fall below that of the control group on further follow-up (Figure 2).

Unlike our study, in which we employ the services of PHWs, an earlier study from rural Southern India had employed trained nurses as VIA providers (8). The demonstration of effectiveness of VIA delivered by PHWs makes screening easily implementable at the grass-roots level in the developing world. Common problems with screening studies in developing countries are poor participation and incomplete data capture (24). We attribute the excellent participation and compliance to diagnosis and treatment in our study to effective health education and easy access to screening, diagnosis, and treatment services. Determinants of participation and compliance in our study have been reported earlier (25,26). The quality assurance of our incidence and mortality data was achieved by meticulous collection and validation. Primary door-to-door data collection was done by MSWs at 24-month intervals, and these data were matched with datasets from Mumbai Cancer Registry and Mumbai Municipal Records. We were therefore able to ensure almost 100% capture of events.

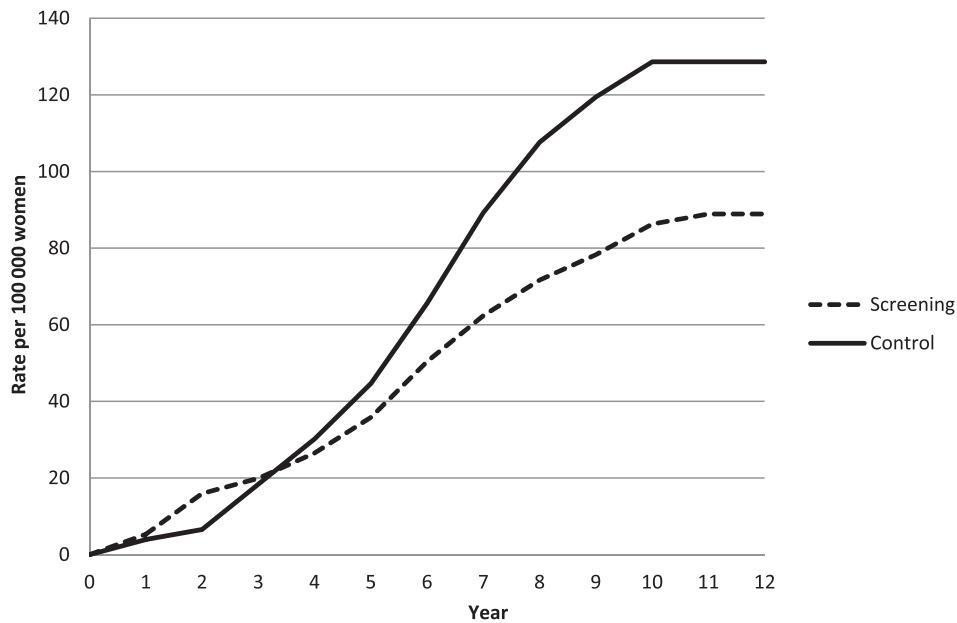
A four-arm cluster-randomized controlled study in rural Western India compared the efficacy of a single round of VIA screening, Pap smear, and human papillomavirus (HPV) DNA testing with standard care. This study reported after 8 years of follow-up that only HPV screening resulted in statistically significant mortality reduction (hazard ratio [HR] = 0.52; 95% CI = 0.33 to 0.83), whereas screening with VIA (HR = 0.86; 95% CI = 0.60 to 1.25) and cytology (HR = 0.89; 95% CI = 0.62 to 1.27) did not result in a statistically significant reduction in mortality from cervical cancer (27). Because it is well known that the majority of HPV infections in young women regress and that HPV testing is an expensive procedure (\$20 to \$30 per test), in a public health context in developing countries, treatment protocols based on HPV screening would raise issues of overdiagnosis in addition to cost.

Although we were able to track all case patients and deaths in both groups through door-to-door monitoring at 24-month intervals and by cross-checking with the Mumbai Cancer Registry and the Mumbai Municipal Death Records, an important limitation of the study is that accurate staging information was not available for 23 case patients from the screening group and 36 case patients from





**Figure 2.** Cumulative incidence curve for cervix cancer. Cumulative incidence of cervical cancer in the screening and control groups after 12 years of follow-up. The screening group recruited 75 360 women aged 35 to 64 years and had an annual attrition of 2.2%, whereas the control group recruited 76 178 women also aged 35 to 64 years and had an annual attrition of 2.3%.



**Figure 3.** Cumulative mortality curve for cervix cancer. Cumulative mortality from cervical cancer in the screening and control groups after 12 years of follow-up. The screening group recruited 75 360 women aged 35 to 64 years and had an annual attrition of 2.2%, whereas the control group recruited 76 178 women also aged 35 to 64 years and had an annual attrition of 2.3%.

the control group. This was mainly on account of nonavailability of clinical or histopathological records for these case patients that were treated at facilities other than the TMH.

Our study provides convincing evidence of the efficacy of VIA performed by PHWs in reducing cervical cancer mortality in limited-resource situations. VIA should be actively advocated for reducing the cervical cancer burden in developing countries. VIA screening has the potential to prevent 22 000 cervical cancer deaths annually in India and 72 600 deaths in resource-poor countries.

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## Notes

S. S. Shastri was responsible for study design, community organization, supervision of community activities, data collection, data analysis, data interpretation, literature search, and writing manuscript. I. Mittra was responsible for conceptualization, study design, community organization, supervision of community activities, data collection, data analysis, data interpretation, and review of manuscript. G. A. Mishra was responsible for community organization, supervision of community activities, data collection, data analysis, and review of manuscript. S. Gupta was responsible for data collection and data analysis. R. Dikshit was responsible for data analysis and review of manuscript. S. Singh was responsible for community organization, supervision of community activities, data collection, and review of manuscript. R. A. Badwe was responsible for tudy design, data analysis, data interpretation, and review of manuscript.

The study sponsors had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

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