The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 2, 2009 VOL. 360 NO. 14

HPV Screening for Cervical Cancer in Rural India

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylla G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.

ABSTRACT

BACKGROUND

In October 1999, we began to measure the effect of a single round of screening by testing for human papillomavirus (HPV), cytologic testing, or visual inspection of the cervix with acetic acid (VIA) on the incidence of cervical cancer and the associated rates of death in the Osmanabad district in India.

METHODS

In this cluster-randomized trial, 52 clusters of villages, with a total of 131,746 healthy women between the ages of 30 and 59 years, were randomly assigned to four groups of 13 clusters each. The groups were randomly assigned to undergo screening by HPV testing (34,126 women), cytologic testing (32,058), or VIA (34,074) or to receive standard care (31,488, control group). Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment.

RESULTS

In the HPV-testing group, cervical cancer was diagnosed in 127 subjects (of whom 39 had stage II or higher), as compared with 118 subjects (of whom 82 had advanced disease) in the control group (hazard ratio for the detection of advanced cancer in the HPV-testing group, 0.47; 95% confidence interval [CI], 0.32 to 0.69). There were 34 deaths from cancer in the HPV-testing group, as compared with 64 in the control group (hazard ratio, 0.52; 95% CI, 0.33 to 0.83). No significant reductions in the numbers of advanced cancers or deaths were observed in the cytologic-testing group or in the VIA group, as compared with the control group. Mild adverse events were reported in 0.1% of screened women.

CONCLUSIONS

In a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer.

From the International Agency for Research on Cancer, Lyon, France (R.S., R.M.); and the Nargis Dutt Memorial Cancer Hospital, Tata Memorial Centre Rural Cancer Project, Barshi (B.M.N., K.J., A.M.B., S.H., S.G.M., R.T., A.K., V.R.K., R.R., N.P.), and the Tata Memorial Centre, Mumbai (S.S.S., R.C., R.K., S.K., S.D., K.A.D.) — both in India. Address reprint requests to Dr. Sankaranarayanan at the International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69008, France, or at sankar@iarc.fr.

N Engl J Med 2009;360:1385-94.

In developing countries, there is a lack of effective screening programs for cervical cancer. In these countries, no clinically significant reduction in the incidence of cervical cancer has occurred during the past three decades.[1-4] In developed countries, by contrast, there has been a major decline in cervical-cancer mortality after the introduction of large-scale cytologic testing. The limited success of such screening in developing countries has stimulated evaluation of testing for human papillomavirus (HPV) and visual inspection of the cervix with acetic acid (VIA).

In October 1999, we initiated a cluster-randomized, controlled trial to evaluate the effectiveness of a single round of HPV testing, cytologic testing, or VIA in reducing the incidence of cervical cancer, as compared with a control group that received usual care in a previously unscreened, high-risk population in the Osmanabad district in the state of Maharashtra, India.[5] We report the cervical-cancer incidence and mortality in the four groups after 8 years of follow-up.

Methods

Study Design

The study design and methods have been described in detail previously.[5] The scientific and ethical review committees of the International Agency for Research on Cancer (IARC) and the Tata Memorial Centre (TMC) and the Nargis Dutt Memorial Cancer Hospital (NDMCH) reviewed and approved the protocol. Clusters of villages consisting of a total of 497 villages in the Osmanabad district that had a primary health care center constituted the randomization unit. A statistician at the IARC who was not involved in the project randomly assigned 52 such clusters to four groups consisting of 13 clusters each. The groups were randomly assigned to receive screening by HPV testing, cytologic testing, or VIA or to receive standard care (control group). Although both practitioners and subjects were aware of study-group assignments, the blinded outcome assessment was performed by cancer-registry personnel in the Osmanabad district. The study was initiated in January 2000, and the results reported here are based on follow-up through December 31, 2007. The study was supported by the Bill and Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention.

Subjects

Eligible women were between the ages of 30 and 59 years, were healthy, were currently or had been married, and were not pregnant. All the women had an intact uterus with no prolapse, had no history of cervical cancer, and were living in the study clusters. The women were identified with the use of household surveys. After explaining the study and obtaining written informed consent, female health workers interviewed the women in each of the four study groups with respect to sociodemographic and reproductive characteristics, using a structured questionnaire. They also instructed all the women about the causes of cervical cancer, signs and symptoms, prevention, early detection, and treatment.

Women in the 13 control clusters were not offered screening but were advised on how to seek screening at local hospitals. Women in the clusters who were assigned to screening were given a card indicating the date, time, and place of screening.

Training

Screening was performed by nine auxiliary nurse–midwives who were trained in a 3-week course with the use of IARC manuals in the collection of cervical cells for HPV testing and cytologic testing and in performing VIA and cryotherapy.[6,7] Nine doctors were trained to supervise the auxiliary nurse–midwives and to perform colposcopy, cryotherapy, and the loop electrosurgical excision procedure (LEEP).[5,7] Two pathologists reviewed the reporting of cervical neoplasms at the TMC. The technicians who were responsible for processing and reading Papanicolaou smears, processing biopsy specimens, and testing for HPV using the Hybrid Capture II test (Qiagen) were trained for 3 months at the TMC.

Screening, Diagnosis, and Treatment

Women were screened in village clinics that were organized in local primary health centers, municipal offices, or schools. The screening process, investigations, and treatments were explained to the women.

In the HPV-testing group, cervical samples, collected in a special transport medium, were processed with the use of the Hybrid Capture II assay for 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) on the basis of the

manufacturer's instructions. A positive result was recorded for specimens with a ratio of the relative light unit to a positive control (RLU/PC) of 1 or more, corresponding to 5000 or more viral copies. In the cytologic-testing group, cervical cells were collected with the use of Cervex brushes, and the smears were processed at NDMCH and reported according to the 1991 Bethesda system.[8] Results for women with atypical squamous cells of uncertain significance or higher-grade lesions were defined as positive. In the VIA group, women with well-defined, dense aceto-white lesions in the cervix, close to the squamocolumnar junction or the os, or aceto-whitening of a cervical growth 1 minute after the application of 4% acetic acid were categorized as VIA-positive.[5,6] Subjects in this group underwent immediate colposcopy and directed biopsies from abnormal areas by a physician in the field clinic and were given appointments for treatment at the NDMCH. Results of HPV testing or cytologic testing were delivered to the subjects within 2 weeks after testing, and those with positive tests were given appointments for colposcopy, biopsy, and treatment.

Women with a positive screening test were evaluated by means of colposcopy, and doctors reported the results as normal findings, inflammation, probable low-grade or high-grade precancerous lesions, or invasive cancer.[7] The colposcopic findings were explained to the women, and punch-biopsy specimens were obtained from abnormal areas. Biopsy specimens were processed at the NDMCH and reported according to typical terminology regarding cervical intraepithelial neoplasia (CIN) grade.[9] Women with colposcopic findings of low-grade or high-grade lesions were offered immediate cryotherapy after the directed biopsy, if all the following criteria were met: the lesion could be covered by the cryoprobe and involved three quadrants or less of the cervix with no extension into the endocervix or vaginal walls, the squamocolumnar junction was fully visible, and there was no suspicion of invasive cancer. LEEP or conization was offered to women with CIN lesions that were unsuitable for cryotherapy. Women with CIN grade 2 or 3 lesions were brought back for cryotherapy or LEEP. Women with suspected invasive cancer were referred to the NDMCH or to the hospital of their choice for investigations and treatment with surgery, radiotherapy, or both.

QUALITY ASSURANCE

Provider competency was maintained by medical supervision in the field and by periodic refresher courses to monitor their performance, along with rates of positive results on screening, correlation between colposcopy and histologic findings, and positive predictive values for CIN.[5] Internal and external quality-control measures were in place for colposcopy and pathological analysis.[5]

OUTCOME MEASURES

The primary outcomes were the incidence of cervical cancer and associated rates of death. Secondary outcomes included stage distribution according to the International Federation of Gynecology and Obstetrics (FIGO) staging system[10] and survival and case fatality rates. Cancer-registry staff members who were unaware of study-group assignments collected data on the date of diagnosis, stage, treatment, and follow-up details for subjects with cervical cancer, using active case-finding methods.[11] Information on all deaths among the subjects was collected from the district death-registration offices, hospital records, and annual house visits. The cause of death for each subject with cervical cancer in the district was assessed by the cancer-registry staff after evaluation of data from hospital records, death certificates, house visits, and interviews of relatives or friends. The screening-project staff then matched the subjects who had incident cervical cancer and those who died with the study database.

STATISTICAL ANALYSIS

The study was designed to have a power of 80% to detect a 50% reduction in the cumulative rate of death from cervical cancer within 15 years after enrollment in one of the intervention groups, as compared with the control group. The death rate from cervical cancer in women between the ages of 30 and 59 years was assumed to be around 20 per 100,000. We assumed that clusters consisting of an average of 2500 women would provide about 25,600 person-years of observation after 15 years (assuming a yearly dropout rate of 2.5%). Taking into account the effect of the intracluster correlation, we assumed a coefficient variation of 0.3 — in other words, the true rates of death from cervical cancer in the control group would vary between 8 and 32 per 100,000. Since this assump-

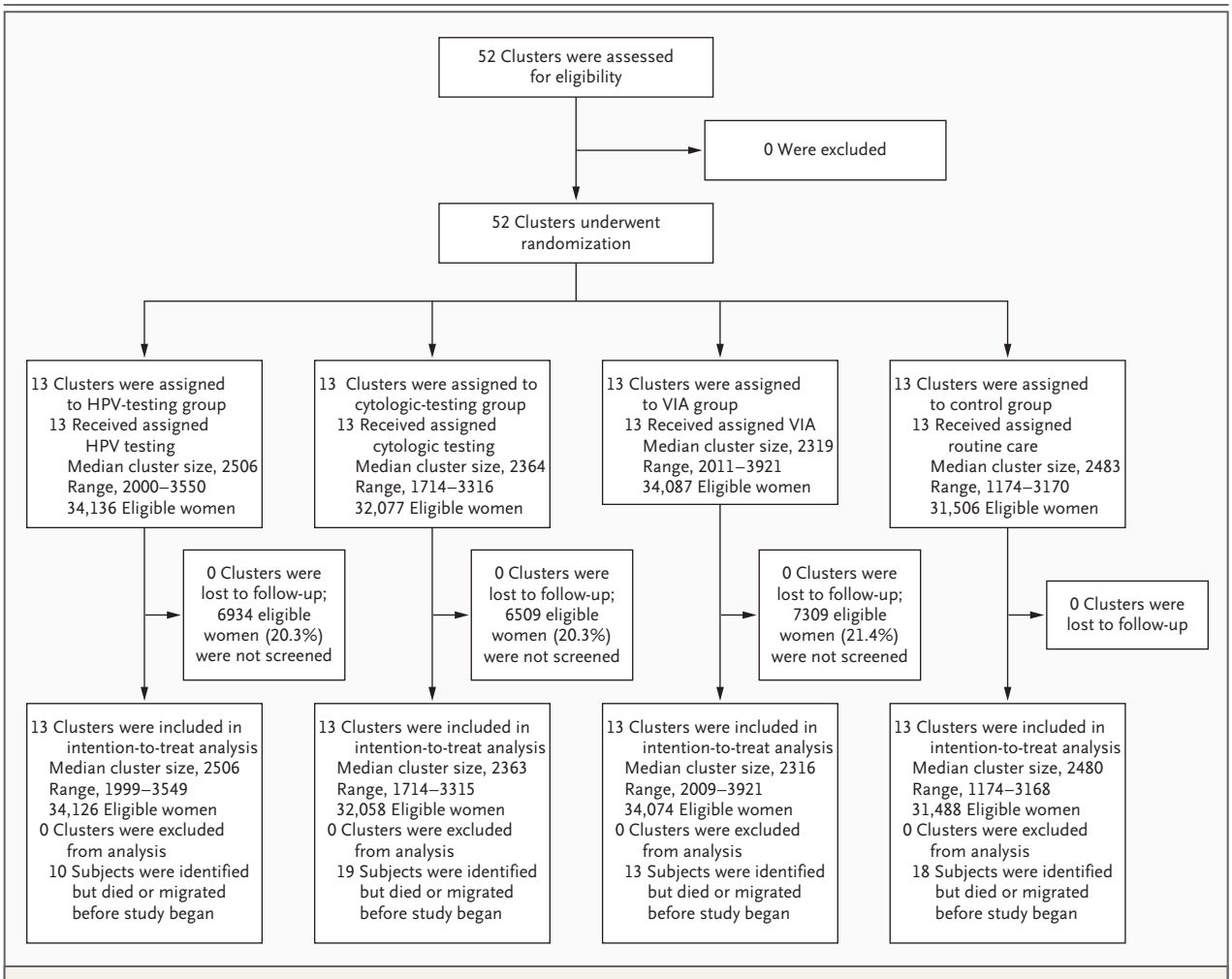

Figure 1. Enrollment and Outcomes.

HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

tion led to a design effect of 1.38, we needed to randomize at least 13 clusters in each study group.[12] The sample-size requirement was satisfied, since each group involved 13 clusters of an average of 2744 women. A P value of less than 0.05 was considered to indicate statistical significance.

Data were entered in an ACCESS database and analyzed with the use of a Stata software package, version 10.0. Analysis was performed according to the intention-to-treat principle: all eligible women in the randomized clusters were included, regardless of their participation in interviews or screening visits. Since the trial used a cluster design, analyses of household and individual characteristics were performed with the use of the cluster as the unit of analysis. Comparisons of cluster proportions or means of household and individual characteristics within the four study groups were performed with the use of the Kruskal–Wallis rank test. Multivariate analysis of the primary outcomes of cervical-cancer incidence and associated mortality was performed with the use of Cox proportional-hazards regression, taking into account the cluster design and with adjustment for age.

The subjects' participation in screening and treatment, rates of positivity on screening, positive predictive values, CIN grades, and cancer-detection rates and stage distribution were calculated as proportions. For the calculation of the incidence of cervical cancer, the numbers of person-years in the intervention groups and the control group were estimated from the date of the study initiation (January 1, 2000) to the date of diagnosis, death, migration, or last follow-up visit, whichever occurred first; for rates of death, the

Table 1. Baseline Characteristics of the Subjects.*

Variable	HPV Testing	Cytologic Testing	VIA	Control	P Value†
Subjects — no.					
All	34,126	32,058	34,074	31,488	
Range	1999–3549	1714–3315	2009–3921	1174–3168	
Living in traditional home with thatched roof					0.77
Subjects — no.	8089	10,291	10,082	8453	
Average proportion in clusters — % (range)	26 (4–72)	33 (3–87)	28 (1–83)	28 (<1–61)	
Age — yr					0.008
Mean	39±0.6	39±0.6	39±0.4	40±0.7	
Range	38–40	39–40	39–40	39–41	
Hindu religion					0.29
Subjects — no.	30,750	28,650	30,197	27,660	
Average proportion in clusters — % (range)	93 (86–98)	93 (79–99)	92 (86–98)	94 (77–100)	
No formal education					0.30
Subjects — no.	22,955	22,259	22,772	18,129	
Average proportion in clusters — % (range)	70 (62–75)	73 (67–78)	70 (61–75)	71 (68–76)	
Working exclusively in the home					0.74
Subjects — no.	20,552	19,470	20,051	14,515	
Average proportion in clusters — % (range)	62 (48–80)	64 (44–79)	62 (54–71)	58 (35–78)	
Currently married					0.84
Subjects — no.	29,601	27,615	29,674	23,095	
Average proportion in clusters — % (range)	90 (88–93)	91 (87–92)	91 (88–93)	91 (88–94)	
No. of pregnancies					0.87
Mean	4.0±0.1	4.0±0.3	4.0±0.2	4.0±0.2	
Range	4–5	4–5	4–5	4–5	

* Plus–minus values are means ±SD. Proportions of subjects are averages of percentages in each 13-unit cluster for each study group. HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.
† P values are for all comparisons among the four study groups.

number of person-years was calculated from the time of study initiation to the date of death, migration, or last follow-up visit, whichever occurred first. Data were censored on December 31, 2007.

RESULTS

SUBJECTS

Of the 131,806 eligible women, 60 died or migrated before the study began; thus, complete data were available for 131,746 eligible women (Fig. 1). The study groups were equally distributed in terms of household type, religion, education, occupation, marital status, and number of pregnancies (Table 1). Only eight of the eligible women had undergone previous cervical screening.

SCREENING AND DETECTION RATES OF CIN

Screening was initiated in January 2000 and was completed by April 2003. Table 2 lists the number of invited and screened women, the number and proportion of positive screen results, and the number of women detected with CIN and cervical cancer according to age. Of the 34,126 women in the HPV-testing group, 27,192 (79.7%) were screened and 2812 (10.3%) had positive results; of the 32,058 women in the cytologic-testing group, 25,549 (79.7%) were screened and 1787 (7.0%) had positive results; and of the 34,074 women in the VIA group, 26,765 (78.5%) were screened and 3733 (13.9%) had positive results. More than 88% of subjects with positive results underwent colposcopy. The detection rate of CIN grade 1 was

Table 2. Rates of Screening, Colposcopy, and Detection of Cervical Intraepithelial Neoplasia (CIN) and Cancer, According to Age Group.*

Variable and Age Group	HPV Testing	Cytologic Testing	VIA
		no./total no. (%)	
Subjects who underwent screening/those who were invited			
30–39 yr	15,340/18,751 (81.8)	14,750/17,823 (82.8)	15,057/18,563 (81.1)
40–49 yr	7628/9503 (80.3)	6981/8796 (79.4)	7547/9578 (78.8)
50–59 yr	4224/5872 (71.9)	3818/5439 (70.2)	4161/5933 (70.1)
All ages	27,192/34,126 (79.7)	25,549/32,058 (79.7)	26,765/34,074 (78.5)
Subjects with positive results on screening			
30–39 yr	1500/15,340 (9.8)	1028/14,750 (7.0)	2681/15,057 (17.8)
40–49 yr	796/7628 (10.4)	493/6981 (7.1)	786/7547 (10.4)
50–59 yr	516/4224 (12.2)	266/3818 (7.0)	266/4161 (6.4)
All ages	2812/27,192 (10.3)	1787/25,549 (7.0)	3733/26,765 (13.9)
Subjects with positive results who underwent colposcopy			
30–39 yr	1358/1500 (90.5)	914/1028 (88.9)	2661/2681 (99.3)
40–49 yr	704/796 (88.4)	420/493 (85.2)	763/786 (97.1)
50–59 yr	443/516 (85.9)	236/266 (88.7)	260/266 (97.7)
All ages	2505/2812 (89.1)	1570/1787 (87.9)	3684/3733 (98.7)
Subjects with CIN grade 1			
30–39 yr	380/15,340 (2.5)	315/14,750 (2.1)	1088/15,057 (7.2)
40–49 yr	164/7628 (2.1)	110/6981 (1.6)	267/7547 (3.5)
50–59 yr	59/4224 (1.4)	51/3818 (1.3)	74/4161 (1.8)
All ages	603/27,192 (2.2)	476/25,549 (1.9)	1429/26,765 (5.3)
Subjects with CIN grade 2 or 3			
30–39 yr	121/15,340 (0.8)	146/14,750 (1.0)	119/15,057 (0.8)
40–49 yr	82/7628 (1.1)	70/6981 (1.0)	50/7547 (0.7)
50–59 yr	42/4224 (1.0)	46/3818 (1.2)	26/4161 (0.6)
All ages	245/27,192 (0.9)	262/25,549 (1.0)	195/26,765 (0.7)
Subjects with cancer diagnosis			
30–39 yr	16/15,340 (0.1)	26/14,750 (0.2)	29/15,057 (0.2)
40–49 yr	30/7628 (0.4)	34/6981 (0.5)	27/7547 (0.4)
50–59 yr	27/4224 (0.6)	23/3818 (0.6)	26/4161 (0.6)
All ages	73/27,192 (0.3)	83/25,549 (0.3)	82/26,765 (0.3)

* HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

higher in the VIA group than in either the HPV-testing group or the cytologic-testing group ($P<0.001$ for both comparisons). The detection rates of CIN grade 2 or 3 lesions and invasive cancer were similar in the three intervention groups ($P=0.06$ for CIN grade 2 and $P=0.16$ for CIN grade 3 for all comparisons). CIN grade 2 or 3 lesions were detected in 245 women in the HPV-testing group, 262 women in the cytologic-testing group, and 195 women in the VIA group. The positive predictive value for detecting CIN grade 2 or 3 lesions was 11.3% in the HPV-testing group, 19.3% in the cytologic-testing group, and 7.4% in the VIA group. The numbers of subjects with CIN grade 1 lesions who underwent treatment were 197 of 603 (32.7%) in the HPV-testing group, 214 of 476 (45.0%) in the cytologic-testing group, and 555 of 1429 (38.8%) in the VIA group; the corresponding numbers for subjects with CIN grade 2 or 3 lesions were 216 of 245 (88.2%), 234 of 262 (89.3%), and 176 of 195 (90.3%).

Of the 31,488 eligible women in the control

Table 3. Distribution of Clinical Stages and Rates of Death, According to Study Group (2000–2007).*

Stage at Diagnosis and Death from Cervical Cancer	HPV Testing	Cytologic Testing	VIA	Control
		no./total no. (%)		
Subjects with positive screening results				NA
Stage at diagnosis				
IA	45/87 (51.7)	58/88 (65.9)	34/91 (37.4)	
IB	25/87 (28.7)	20/88 (22.7)	19/91 (20.9)	
≥II	14/87 (16.1)	10/88 (11.4)	35/91 (38.5)	
Unknown	3/87 (3.4)	0	3/91 (3.3)	
Death from cervical cancer	12/87 (13.8)	18/88 (20.5)	27/91 (29.7)	
Subjects with negative screening results				NA
Stage at diagnosis				
IA	0	2/22 (9.1)	1/25 (4.0)	
IB	2/8 (25.0)	4/22 (18.2)	4/25 (16.0)	
≥II	5/8 (62.5)	15/22 (68.2)	19/25 (76.0)	
Unknown	1/8 (12.5)	1/22 (4.5)	1/25 (4.0)	
Death from cervical cancer	0	9/22 (40.9)	8/25 (32.0)	
Subjects not screened				NA
Stage at diagnosis				
IA	2/32 (6.2)	0	0	
IB	6/32 (18.8)	5/42 (11.9)	8/41 (19.5)	
≥II	20/32 (62.5)	33/42 (78.6)	32/41 (78.0)	
Unknown	4/32 (12.5)	4/42 (9.5)	1/41 (2.4)	
Death from cervical cancer	22/32 (68.8)	27/42 (64.3)	21/41 (51.2)	
All subjects assigned to undergo screening				NA
Stage at diagnosis				
IA	47/127 (37.0)	60/152 (39.5)	35/157 (22.3)	
IB	33/127 (26.0)	29/152 (19.1)	31/157 (19.7)	
≥II	39/127 (30.7)	58/152 (38.2)	86/157 (54.8)	
Unknown	8/127 (6.3)	5/152 (3.3)	5/157 (3.2)	
Death from cervical cancer	34/127 (26.8)	54/152 (35.5)	56/157 (35.7)	
Subjects with symptoms at diagnosis	NA	NA	NA	
Stage at diagnosis				
IA				7/118 (5.9)
IB				26/118 (22.0)
≥II				82/118 (69.5)
Unknown				3/118 (2.5)
Death from cervical cancer				64/118 (54.2)

* HPV denotes human papillomavirus, NA not applicable, and VIA visual inspection of the cervix with acetic acid.

group, 1946 (6.2%) requested screening and were tested with cytologic testing; of these subjects, 15 CIN grade 2 or 3 lesions were detected, and 41 subjects had invasive cancer (18% in stage I and 58% in stage III).

CERVICAL CANCER INCIDENCE AND MORTALITY

The numbers of cervical cancers that were detected on screening (i.e., those that were diagnosed within 3 months after positive results) were 73 in the HPV-testing group, 83 in the cytologic-testing

Table 4. Incidence of Cervical Cancer and Rates of Death.*

Variable	HPV Testing	Cytologic Testing	VIA	Control
Incidence of all cervical cancer — no.	127	152	157	118
Person-yr of follow-up — no.	268,185	250,523	267,326	247,895
Rate per 100,000 person-yr	47.4	60.7	58.7	47.6
Hazard ratio (95% CI)	1.05 (0.77–1.43)	1.34 (0.99–1.82)	1.30 (0.95–1.78)	1.00
Incidence of stage II or higher cervical cancer — no.	39	58	86	82
Person-yr of follow-up — no.	268,185	250,523	267,326	247,895
Rate per 100,000 person-yr	14.5	23.2	32.2	33.1
Hazard ratio (95% CI)	0.47 (0.32–0.69)	0.75 (0.51–1.10)	1.04 (0.72–1.49)	1.00
Death — no.	34	54	56	64
Person-yr of follow-up — no.	268,674	251,144	267,917	248,175
Rate per 100,000 person-yr	12.7	21.5	20.9	25.8
Hazard ratio (95% CI)	0.52 (0.33–0.83)	0.89 (0.62–1.27)	0.86 (0.60–1.25)	1.00

* Rates and hazard ratios have been adjusted for age. Hazard ratios are for the comparison between each intervention group and the control group. CI denotes confidence interval, HPV human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

group, and 82 in the VIA group. The numbers of subsequent incident cancers (i.e., those that were diagnosed 3 months after positive results on screening or among women who had received negative results) were 22 in the HPV-testing group, 27 in the cytologic-testing group, and 34 in the VIA group. The proportions of cancers that were detected in stage I were about 60% in the HPV-testing and cytologic-testing groups, 42% in the VIA group, and 28% in the control group (Table 3).

There were 34 deaths from cervical cancer in the HPV-testing group, 54 in the cytologic-testing group, 56 in the VIA group, and 64 in the control group (Table 3). The incidence rate of cervical cancer of stage II or higher and death rates from cervical cancer were significantly higher in the cytologic-testing group and the VIA group than in the HPV-testing group. In the HPV-testing group, the hazard ratio for the detection of advanced cancer was 0.47 (95% confidence interval [CI], 0.32 to 0.69) and the hazard ratio for death was 0.52 (95% CI, 0.33 to 0.83), as compared with the control group (Table 4). During the 8-year follow-up period, invasive cervical cancer developed in 8 of 24,380 HPV-negative women, in 22 of 23,762 women who had negative results on cytologic testing, and in 25 of 23,032 women who had negative results on VIA, with age-standardized rates of 3.7, 15.5, and 16.0 cases of invasive cervical cancer per 100,000 person-years, respectively.

Figure 2 shows the cumulative incidence of cervical cancer, rates of stage II or higher disease, and cumulative mortality. The cumulative incidence of advanced cervical cancer and the cumulative rate of death were lower in the HPV-testing group than in the control group, and the gap widened throughout the follow-up period. There was no significant reduction in the rate of death from any cause in the intervention groups, as compared with the control group (data not shown).

Among the women who were screened and treated, mild adverse events were reported in 123 women, and a severe adverse event of uncontrolled bleeding after LEEP that resulted in hysterectomy was reported in 1 woman.

DISCUSSION

In our cluster-randomized, controlled trial, a screening program for the detection of cervical cancer was accomplished in a low-resource setting. Since there is little screening for cervical cancer in India, women who did not undergo screening (control group) were considered to receive the standard of care. The inclusion of this control group was approved by the IARC and Indian institutional ethics committees.

The difference in the number of eligible women that were reported previously[5] and the number reported here was due to the erroneous inclusion of ineligible women in the original report and updates of data. The randomization of groups of women in clusters minimized the possibility that those assigned to one study group would receive the intervention provided to another study group.

Our study found that a single round of HPV testing was associated with a significant decline in the rate of advanced cervical cancers and associated deaths, as compared with the unscreened control group. By contrast, there was no significant reduction in the rate of death in either the cytologic-testing group or the VIA group, as compared with the control group. The age-standardized rate of invasive cancer among women who had negative results on cytologic testing or VIA was more than four times the rate among HPV-negative women, indicating a high negative predictive value associated with a negative HPV test. The reduction in the incidence of advanced cancers and deaths associated with HPV testing probably reflects the higher sensitivity of HPV testing to detect lesions with a high potential for malignant transformation than that of cytologic testing or VIA.

No reduction in the rate of cervical cancer was observed in the VIA group in our study, whereas the procedure was associated with a 25% reduction in cervical-cancer incidence and a 35% reduction in mortality in a randomized trial in South India.[13] The reason for these differences in outcomes between the two studies is unknown but may be due to the higher rate of treatment in the South Indian trial.

We found that HPV testing was the most objective and reproducible of all cervical screening tests and was less demanding in terms of training and quality assurance. In low-resource settings with no capacity for colposcopy and histopathological analysis (e.g., many countries in sub-Saharan Africa), HPV-positive women without clinical evidence of invasive cancer could receive immediate treatment, such as cryotherapy.[14] However, since most HPV infections in young women regress rapidly without causing clinically significant disease, such an approach raises a legitimate concern. Hence, HPV testing should not be used for primary screening of women under 30 years of age.

A drawback to HPV testing is that it is more expensive ($20 to $30 per test, in U.S. dollars) and time-consuming than other screening tests, and it requires a sophisticated laboratory infrastructure. A simple, affordable, and accurate HPV test

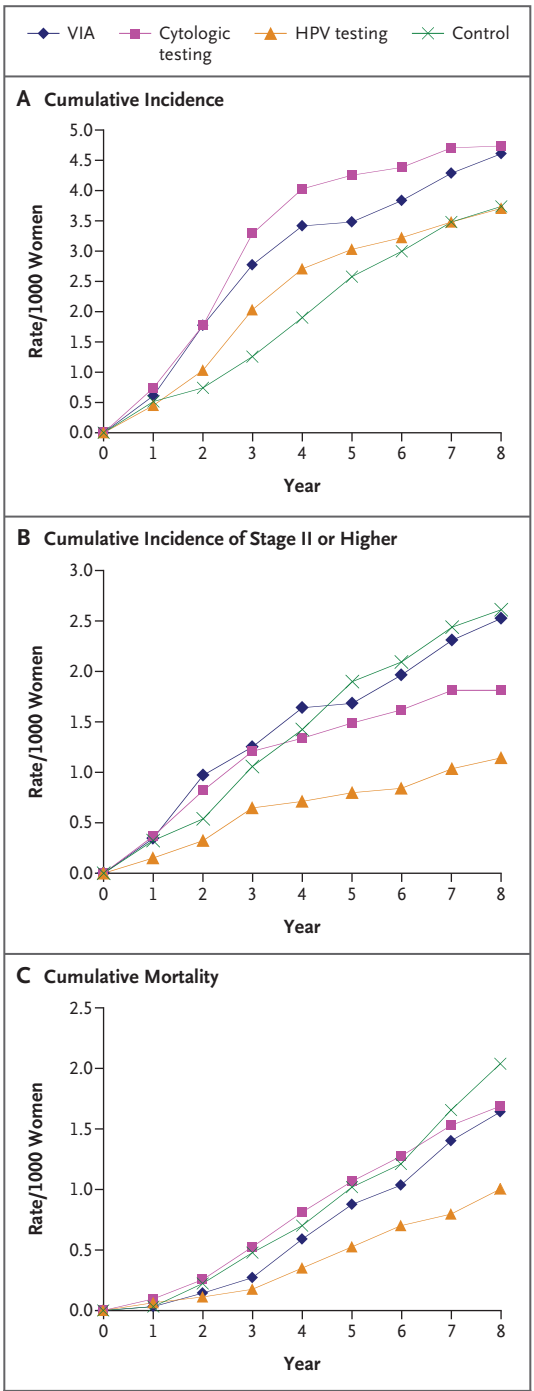

Figure 2. Cumulative Incidence of Cervical Cancer of Any Stage (Panel A) and Stage II or Higher (Panel B) and Cumulative Mortality (Panel C).

HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

(careHPV test, Qiagen) that provides results within 3 hours was evaluated in China, and its accuracy was similar to that of the Hybrid Capture II test that we used in our study. The careHPV test had higher sensitivity than VIA (90.2% vs. 41.4%) but a lower specificity (84.2% vs. 94.5%).[15] The careHPV test is expected to be commercially available in developing countries in the near future. Our results, combined with those of the Chinese study of the new HPV test, indicate that HPV testing is appropriate as a primary screening approach in low-resource settings for women who are at least 30 years of age.[15]

Supported by the Bill and Melinda Gates Foundation, through the Alliance for Cervical Cancer Prevention.

No potential conflict of interest relevant to this article was reported.

We thank the women who participated in this study and their families; the Ministry of Health, Government of Maharashtra; the Department of Atomic Energy, Government of India; the Osmanabad district collectors, Zilla Parishad chief executive officers, district health officers, and other administrative authorities; staff members of local health services, numerous women's organizations, voluntary organizations, and civic leaders in the project area who facilitated the conduct of the study; Dr. Peter Boyle, IARC director from 2004 through 2008; Dr. René Lambert, IARC visiting scientist; Dr. Catherine Sauvaget, IARC scientist; Drs. Stephen Duffy, Peter Sasieni, and Jack Cuzick of Cancer Research U.K., Wolfson Institute of Preventive Medicine, London, for their useful advice and comments on early versions of the manuscript; Dr. D.M. Parkin of the Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, United Kingdom, for his support and assistance in the design and the monitoring of the study and for his useful comments; Dr. John Sellors of the Program for Appropriate Technology in Health (PATH), Seattle; Drs. Ramani Wesley and Somanathan Thara of the Regional Cancer Centre, Trivandrum, India; Dr. Partha Basu of the Chittaranjan National Cancer Institute, Kolkata, India; Dr. Daniel Seigneurin of University Hospital, Grenoble, France; Dr. L. Frappart of the Edouard Herriot Hospital and Dr. B. Fontanière of the Centre Leon Berard (both in Lyon, France) for their assistance in training and quality control of various study inputs; our colleagues in TMC, NDMCH, and IARC who helped us in several project-related inputs; and Mrs. Evelyn Bayle of the IARC Screening Group for her help in the preparation of the manuscript.

REFERENCES

1. Ferlay J, Parkin DM, Pisani P. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase no. 5, version 2.0. Lyon, France: IARC Press, 2004.
2. Curado MP, Edwards BK, Shin HR, et al., eds. Cancer incidence in five continents. Vol. IX (9). Lyon, France: IARC Press, 2007. (IARC scientific publications no. 160.)
3. Sankaranarayanan R, Budukh A, Rajkumar R. Effective screening programs for cervical cancer in low- and middle-income developing countries. Bull World Health Organ 2001;79:954-62.
4. Cervix cancer screening. Vol. 10. IARC handbooks on cancer prevention. Lyon, France: IARC Press, 2005.
5. Sankaranarayanan R, Nene BM, Dinshaw KA, et al. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. Int J Cancer 2005;116:617-23.
6. Sankaranarayanan R, Wesley RS. A practical manual on visual screening for cervical neoplasia. Lyon, France: IARC Press, 2003. (IARC technical publication no. 41.)
7. Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon, France: IARC Press, 2003.
8. Kurman RJ, Malkasian GD Jr, Sedlis A, Solomon D. From Papanicolaou to Bethesda: the rationale for a new cervical cytologic classification. Obstet Gynecol 1991;77:779-82.
9. Tavassoli FA, Devilee P, eds. World Health Organization classification of tumours. Vol. 5. Pathology and genetics of tumours of the breast and female genital organs. Lyon, France: IARC Press, 2003.
10. Hermanek P, Sobin H, eds. TNM classification of malignant tumours. 4th ed. Geneva: Springer-Verlag, 1987:13-8.
11. Jensen OM, Parkin DM, Maclennan R, Muir CS, Skeet RG. Cancer registration principles and methods. Lyon, France: International Agency for Research on Cancer, 1991. (IARC scientific publications no. 95.)
12. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. Int J Epidemiol 1999;28:319-26.
13. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet 2007;370:398-406.
14. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC Jr. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. JAMA 2005;294:2173-81.
15. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. Lancet Oncol 2008;9:929-36.