COMPARATIVE EFFICACY OF VISUAL INSPECTION WITH ACETIC ACID (VIA), HPV TESTING AND CONVENTIONAL CYTOLOGY IN CERVICAL CANCER PREVENTION: A CLUSTER RANDOMISED CONTROLLED SCREENING TRIAL IN OSMANABAD DISTRICT, MAHARASHTRA, INDIA

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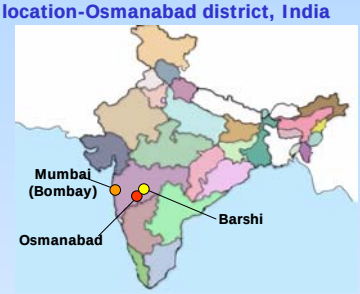
Background

The impact of screening by visual inspection with acetic acid (VIA), cytology, or human papillomavirus (HPV) testing on cervical cancer incidence and mortality is being investigated in a cluster randomised controlled trial in India. Women aged 30-59 years in 52 clusters of 497 villages in Osmanabad District, India, were randomised to a single round of screening by trained midwives with either VIA (N=34,149), cytology (N=32,136), HPV testing (N=34,515) or to a control group (N=30,378). All laboratory tests were performed locally. Test-positive women had further investigations (colposcopy/biopsy) and treatment in the base hospital. Data on participation, test positivity, cervical intraepithelial neoplasia (CIN) detection and treatment rates were analysed. We report the preliminary findings after the screening phase here (Feb. 2000 – Nov. 2003).

Study location-Osmanabad district, India



Notional map showing Osmanabad district, Maharashtra, India

Objectives

- To evaluate the extent of reduction in incidence of and mortality from cervical cancer associated with a single round of screening by one of the following screening methods, as compared to a control group receiving usual care.
  - Visual inspection after application of 4% Acetic Acid (VIA)
  - Conventional cytology
  - HPV DNA testing by Hybrid capture II method
- To evaluate the cost-effectiveness (CE) of once a lifetime screening by VIA, cytology and HPV testing based on real data generated from the study.

Definition of screen positivity

- VIA: Well-defined acetowhite lesions on the cervix near/in the transformation zone
- Cytology: Atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), invasive cancer
- HPV testing: ≥ 1 RLU by HC II (>5000 viral DNA copies)

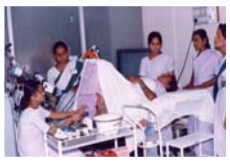
Methodology

Cluster randomised controlled trial

- 52 Primary health centers randomised into 3 intervention arms (VIA, cytology, HPV testing) and one control arm.
- 34,000 eligible women (30-59 years) in each arm

Field procedures

Enumeration and interview



Health Education — Screening Clinic

Field procedures (continued)

- Enumeration of all women and listing of eligible women (30-59 years);
- Interview and informed consent of eligible women;
- Educational programmes and preparation for screening clinics;
- Screening in village clinics;
- Colposcopy/biopsy of VIA-positive women;

Procedures at the NDMCH

Pathology laboratory

Screening and Treatment Equipment

- Cytology and HPV testing in NDMCH laboratories
- Colposcopy/biopsy of cytology and HPV-positive women
- Treatment of CIN with cryotherapy/LEEP/conization
- Treatment of women with invasive cancer by surgery/radiotherapy
- Clinical follow-up of treated women

Control Arm

- Eligible women enumerated and interviewed;
- No screening clinics;
- Informed about cervical cancer symptoms, signs and treatment options;
- Free screening and treatment facility to cervical cancer patients at NDMCH.

Process measures

- Coverage per screening, investigations and treatment

Intermediate outcome measures

- Detection rates of cervical intraepithelial neoplasia (CIN) and cancer;
- Stage distribution of cervical cancer;
- Case fatality and survival from cancer.

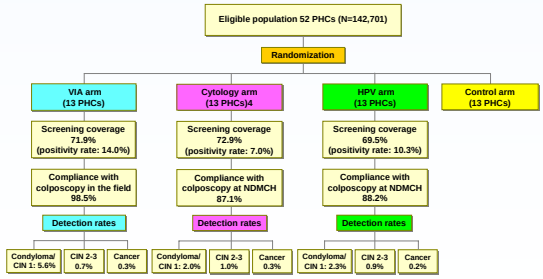
Final endpoint

- Reduction in incidence of and mortality from cervical cancer.

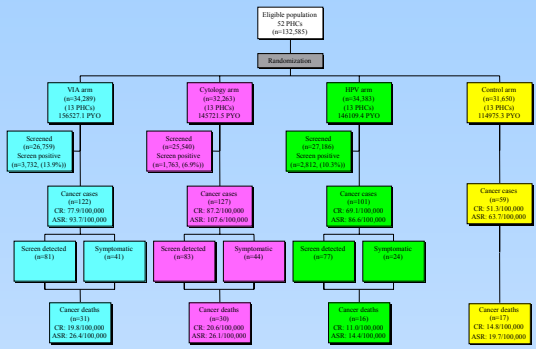
Follow-up: Active and passive methods

- Linkage with population-based cancer registry;
- Linkage with mortality data;
- Active enumeration of the participants for events by house visits.

Preliminary results after the screening phase



Follow-up results after the screening phase



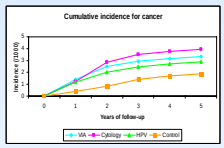
Stage distribution by detection mode

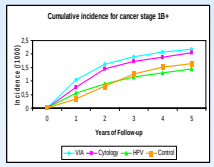
Group	Detection mode	Stage 1A (%)	Stage 1B (%)	Stage 2+ (%)	Unknown (%)	Total
Control	Symptomatic	3 (5.1)	13 (22.0)	39 (66.1)	4 (6.8)	59
HPV	Symptomatic	1 (4.2)	5 (20.8)	14 (58.3)	4 (16.7)	24
	Screening	36 (46.8)	21 (27.3)	10 (13.0)	10 (13.0)	77
	Total	37 (36.6)	26 (25.7)	24 (23.8)	14 (13.9)	101
Cytology	Symptomatic	1 (2.3)	4 (9.1)	35 (79.5)	4 (9.1)	44
	Screening	40 (48.2)	20 (24.1)	7 (8.4)	16 (19.3)	83
	Total	41 (32.3)	24 (18.9)	42 (33.1)	20 (15.7)	127
VIA	Symptomatic	1 (2.4)	8 (19.5)	26 (63.4)	6 (14.6)	41
	Screening	33 (40.7)	16 (19.8)	30 (37.0)	2 (2.5)	81
	Total	34 (27.9)	24 (19.7)	56 (45.9)	8 (6.6)	122

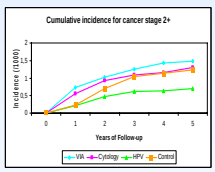
Relative hazard ajusted for age, parity, cluster design

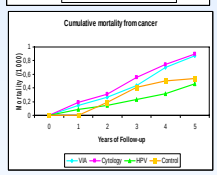
Group	Relative hazard (95% CI) for end point			
	Cervical cancer incidence	Stage 1B+	Stage 2+	Cervical cancer death
Control	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
HPV	1.50 (1.03-2.17)	0.79 (0.53-1.17)	0.50 (0.28-0.91)	0.62 (0.30-1.32)
Cytology	1.84 (1.26-2.70)	1.00 (0.62-1.63)	0.82 (0.46-1.47)	1.02 (0.57-1.85)
VIA	1.62 (1.07-2.45)	1.12 (0.67-1.86)	1.03 (0.60-1.76)	1.00 (0.56-1.81)

Cumulative incidence and mortality









Conclusions

- VIA detected significantly more CIN 1 than HPV testing and cytology while CIN 2-3 detection rates are similar for all three tests;
- All three modalities detected large numbers of prevalent cancers, with incidence rates 5-6 times those expected incidence in the absence of screening;
- There was considerable clinical under-diagnosis of invasive cancers in the control group and hence very prolonged follow-up may be required for control group to 'catch up' and to obtain a reliable estimate of the effects of the screening on incidence and mortality as compared to the control group;
- Harvest of prevalent tumours at screening included large numbers of early stage tumours and relatively small proportions of advanced stage as compared to the control group;
- Control group caught up considerably more rapidly for incidence of advanced stage cancers than for incidence of cervical cancer overall;
- At stage 2 or worse, HPV group showed a 50% significant reduction in incidence and a non significant reduction in mortality;
- No significant effect of screening on mortality was observed for any screening modality until now;
- Reduction in advanced disease for two out of the three modalities suggests that in future, benefits will be observed in terms of advanced stage disease and mortality.

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