Selected Summaries

HPV screening for cervical cancer in rural India: Do we have an answer?

Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, Dinshaw KA. (International Agency for Research on Cancer, Lyon, France; the Nargis Dutt Memorial Cancer Hospital, Tata Memorial Centre Rural Cancer Project, Barshi; and the Tata Memorial Centre, Mumbai, India.) HPV screening for cervical cancer in rural India. *N Engl J Med* 2009;**360:**1385–94.

SUMMARY

This randomized clinical trial was conducted to study the impact of a single round of screening using human papillomavirus (HPV) testing on the incidence of and mortality from cervical cancer. The study enrolled 131 746 women living in 497 villages in Osmanabad district, Maharashtra, India. The study population was divided into 52 clusters and randomized into 4 groups (each with 13 clusters). Three groups were screened for cervical cancer using one of the following methods—HPV testing by the Hybrid Capture 2 (hc2) test (Qiagen Gaithersburg Inc., USA), conventional cervical cytology or VIA (visual inspection with acetic acid); and the fourth (control) group was given standard care.

Response to the screening programme was good—about 79% of women participated in each of the 3 groups. Screen-positive rates in each of the groups were: HPV testing 10.3%; cytology 7%; and VIA 13.9%. Women who were screen-positive underwent colposcopy with directed biopsy and further treatment based on the histopathology report. All participants were followed for 8 years.

The incidence of advanced stage cervical cancer (stage II or higher) and death rates from cervical cancer were significantly lower in the HPV testing group compared with the other 3 groups. The hazard ratio for detection of advanced cancer was 0.47 (95% CI 0.32–0.69) and for death was 0.52 (95% CI 0.33–0.83) compared with the control group. Over the 8 years of follow up, invasive cervical cancer was diagnosed despite negative results on screening in 8 of 24 380 women in the HPV testing group, 22 of 23 762 women in the cytology group and 25 of 23 032 women in the VIA group, which yielded age-standardized rates of 3.7, 15.5 and 16.0 cases of invasive cervical cancer per 100 000 person-years in the 3 groups, respectively. Also, there were cervical cancer-related deaths in screen-negative women: 9 in the cytology group and 8 in the VIA group, but none in women after a single HPV-negative result over 8 years of follow up. The authors concluded that in developing countries with low-resource settings, a single round of HPV testing was associated with a significant reduction in advanced stage cervical cancers as well as deaths due to the disease.

COMMENT

For the past 50 years, cervical cytology has been the cornerstone of prevention for cervical cancer programmes globally. In developed countries such as the USA, widespread cytology-based screening has reduced the rates of invasive cancer cervix by 74%.[1] However, the Pap smear has a low sensitivity (about 50%)[2] although a high specificity. Screening programmes based on cytology compensate for the high false-negative rate by frequent screening. Such programmes must therefore ensure compliance, coverage and quality, which is not feasible in low-resource settings. Thus, cytology-based screening in India is only opportunistic and has not made any significant impact on the burden of cervical cancer.

With the understanding that persistent infection with high risk HPV types is a cause of cervical cancer, the role of HPV DNA testing in screening for cervical cancer has received considerable attention. HPV testing has 20%–40% greater sensitivity but 5%–10% lower specificity than the Pap smear.[3] Women who are high risk HPV DNA-negative appear to be protected against CIN 3+ for up to 10 years (high negative predictive value).[4] Also, HPV testing is the most objective and reproducible of all cervical screening methods. In late adolescent and young women, most HPV infections are transient, so HPV positivity rates are high and do not signify high risk. Testing for HPV in this group is not indicated. However, persistence of HPV infection in women $\geq$30 years of age implies high risk for cervical cancer and this should be the target group for screening.

Ample evidence from numerous studies suggests that it is probably time to shift from cytology-based to HPV-based screening programmes.[2,5] Cytology may be used to triage HPV-positive women to colposcopy. Interim guidance for the use of HPV DNA testing as an adjunct to cytology for screening suggests that HPV DNA-positive, cytology-negative women can be re-tested in 12 months with both cytology and HPV testing, and there is no need for colposcopy. Persistent HPV infection requires colposcopy.[6] Because of improved sensitivity, HPV-based screening can be done once in 5 years rather than 3 years. Developed countries with a proper cytology-based screening programme may be able to shift to a better method of screening based on HPV testing at less frequent intervals. This still does not solve the problem for developing countries where it is difficult to ensure screening at regular intervals.

Sankaranarayanan *et al*. have shown in a cluster-randomized controlled trial in a low-resource setting in rural India that a single round of HPV testing reduced the rate of advanced cervical cancers and associated deaths compared with the unscreened control group over 8 years of follow up. Also, a single round of cytological testing or VIA in a similar setting was not associated with a significant reduction in the rates of advanced cervical cancer and related deaths. The age-standardized rate of invasive cancer among screen-negative women was almost 4 times lower in HPV-negative women compared with cytology-negative and VIA-negative women, indicating that a single negative HPV test had a high negative predictive value.

The study design is worthy of mention as it has several unique aspects. It was based in a rural area where there was no proper screening system in place and included married women in the target age group of 30–59 years so that the results could be applied to developing countries. The impact of one-time screening has been evaluated, which may be of value for implementation in low-resource settings. Bias was eliminated by randomizing the clusters of villages and blinding investigators who collected data regarding the incidence of and mortality from cervical cancer. The staff conducting the screening tests were adequately trained and supervised, and their performance was monitored periodically.

Also, quality control measures were in place for the cytology and histopathological analysis to ensure optimum results. Care was taken before designing the study to calculate the sample size to give a power of 80% to detect a 50% decline in cumulative death rates due to cervical cancer. Also, allowance was made for loss to follow up.

This study has major implications for countries such as India where resources are scarce and there is a major difficulty in ensuring repeated screening at regular intervals, so it is important to chalk out alternative low-cost and effective strategies. VIA performed by health workers is the least expensive of all screening options. This study did not find a reduction in the rate of cervical cancer with VIA, although a previous randomized trial from southern India had found a 25% reduction in the incidence of cervical cancer and a 35% reduction in mortality.[7] VIA is an operator-dependent method with high inter-observer variation, which requires proper quality control and training-assessment protocols. HPV testing has emerged as a superior test with greater sensitivity, accuracy and objectivity. Presently, the drawback is that the hc2 method is very expensive. However, a rapid affordable test is expected to be available by 2011.[8,9] Thus, implementation of a nationwide programme of once-in-a-lifetime HPV testing at 40 years of age holds promise for reducing the burden of cervical cancer. An appropriate protocol for management of HPV-positive women must be developed. In areas with very high prevalence, colposcopy of all patients may not be cost-effective or feasible. VIA may be used to triage patients. In some regions, screen-and-treat protocols using cryotherapy for HPV-positive women (>30 years of age) without clinical evidence of invasive cancer may minimize cost and loss to follow up, especially if there are no facilities for colposcopy and histopathological analysis.[10] Proper implementation of this strategy in developing countries could save the lives of countless women in the years to come.

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Screening for cancer of the prostate: Do we have an answer?

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