CORRESPONDENCE

HPV Screening for Cervical Cancer in Rural India

TO THE EDITOR: Sankaranarayanan et al. (April 2 issue)[1] report no significant differences in rates of detection of high-risk cervical neoplasia among women who underwent screening by cytologic testing, testing for human papillomavirus (HPV) with the Hybrid Capture II assay, or visual inspection of the cervix with acetic acid (VIA). Reductions in mortality from cervical cancer were observed only among women screened by HPV testing. The unexpected lack of a correlation between detection rates reported for the screening tests and subsequent mortality rates requires careful consideration. Sankaranarayanan et al. acknowledge that unidentified differences in follow-up care, rather than differences in the performance of screening tests, account for differences in mortality between women screened by VIA in their current study and women screened by VIA in an earlier study.[2] The same logic, applied to the current data, suggests that unidentified differences in follow-up care, rather than nonsignificant differences among screening-test detection rates, account for differences in mortality among the groups of women who underwent screening. Within the political structures of many developing countries, there is genuine lack of support for cervical-cancer prevention efforts,[3] which may be further eroded by the questionable conclusion that only an unaffordable screening option is better than none at all.[1]

Eric J. Suba, M.D.
Kaiser Permanente Medical Center
San Francisco, CA 94115
eric.suba@kp.org

Edmund S. Cibas, M.D.
Harvard Medical School
Boston, MA 02115

Stephen S. Raab, M.D.
University of Colorado Health Sciences Center
Aurora, CO 80045

1. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med 2009;360:1385-94.
2. 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.
3. Suba EJ, Murphy SK, Donnelly AD, Furia LM, Huynh ML, Raab SS. Systems analysis of real-world obstacles to successful cervical cancer prevention in developing countries. Am J Public Health 2006;96:480-7.

TO THE EDITOR: The study by the Indian Council of Medical Research showed that a down-staging effect of VIA and a reduction in the case fatality rate still hold in the Indian subcontinent.[1] The discrepancy between the authors' earlier findings and the current findings with regard to the benefits of VIA calls for more explanation.[2]

Jain Ankit, M.D.
Kidwai Memorial Institute of Oncology
Bangalore 560030, India
ankitjaindm@gmail.com

Jain Prakriti, M.B., B.S., D.G.O.
Bhagwan Mahaveer Jain Hospital
Bangalore 560052, India

K.C. Lakshmaiah, M.D., D.M.
Kidwai Memorial Institute of Oncology
Bangalore 560030, India

THIS WEEK'S LETTERS

1. Singh V, Sehgal A, Luthra UK. Screening for cervical cancer by direct inspection. BMJ 1992;304:534-5.
2. 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.

TO THE EDITOR: In a previous article,[1] Sankaranarayanan et al. reported a decrease in cervical-cancer mortality with the use of VIA and the "screen and treat" approach, whereas the current article calls for multiple visits and treatment only of women with grade 2 or 3 cervical intraepithelial neoplasia confirmed on biopsy. In the current report, there is no discussion of this difference between the two studies.

The current data cast doubt on VIA, which is an invaluable asset to cervical-cancer prevention in developing countries. The benefit of VIA in low-resource settings is that it can be used to detect cervical precancer inexpensively and that it enables the examiner to institute immediate and appropriate therapy. This strategy decreases the risk that a patient with a potentially precancerous lesion will be lost to follow-up.

We strongly believe that the lack of survival benefit reported in the current article should not preclude the lifesaving results of screen-and-treat programs that have been demonstrated previously.

Miriam L. Cremer, M.D., M.P.H.
Basic Health International
San Salvador, El Salvador
mlcremer@hotmail.com

Elizabeth Conlisk, Ph.D.
Hampshire College
Amherst, MA 01002

Juan C. Felix, M.D.
University of Southern California
Los Angeles, CA 90033

Dr. Felix reports receiving lecture fees from Qiagen and Hologic. No other potential conflict of interest relevant to this letter was reported.

1. 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.

TO THE EDITOR: Interest in implementing cervical-cancer prevention services in developing nations will probably peak as a result of the powerful evidence reported by Sankaranarayanan et al. Unfortunately, expenditures on health care and health care–related development assistance may shrink because of the ongoing global financial downturn.[1] In this scenario, the integration of cervical-cancer prevention services with other population-based health care programs may provide valuable opportunities for cost-effective initiation, expansion, and sustainability of these services.

Programs for the prevention and treatment of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are being implemented in many developing nations, where cervical-cancer incidence and mortality rates are also high. HIV–AIDS programs are slowly but substantially contributing to improved health infrastructures and increasing access to health care.[2] Integration of cervical-cancer prevention services within HIV–AIDS programs is an excellent opportunity to target women at highest risk for cervical cancer, as we recently showed in Zambia.[3,4] Such efforts hold the promise of both saving lives from an eminently preventable cancer and strengthening the broader primary care context that is so essential for the sustainability of vertical health programs.

Mulindi H. Mwanahamuntu, M.B., B.S., M.Med.
University Teaching Hospital
Lusaka, Zambia

Vikrant V. Sahasrabuddhe, M.B., B.S., Dr.P.H.
Vanderbilt University Institute for Global Health
Nashville, TN 37203
vikrant.sahasrabuddhe@vanderbilt.edu

Groesbeck P. Parham, M.D.
Center for Infectious Disease Research in Zambia
Lusaka, Zambia

1. Parry J, Humphreys G. Health amid a financial crisis: a complex diagnosis. Bull World Health Organ 2009;87:4-5.
2. El-Sadr WM, Hoos D. The president's emergency plan for AIDS relief — is the emergency over? N Engl J Med 2008;359:553-5.
3. Mwanahamuntu MH, Sahasrabuddhe VV, Pfaendler KS, et al. Implementation of 'see-and-treat' cervical cancer prevention services linked to HIV care in Zambia. AIDS 2009;23:N1-N5.
4. Pfaendler KS, Mwanahamuntu MH, Sahasrabuddhe VV, Mudenda V, Stringer JS, Parham GP. Management of cryotherapy-ineligible women in a "screen-and-treat" cervical cancer prevention program targeting HIV-infected women in Zambia: lessons from the field. Gynecol Oncol 2008;110:402-7.

TO THE EDITOR: Sankaranarayanan et al. found that a single DNA screening test for cervical-cancer–related HPV strains can be cost-effective in a resource-limited setting. An additional strategy could stretch a public health budget even fur-

ther, increasing the number of early cancers detected by extending screening to more women. In 1943, Dorfman[1] proposed a clever pooling approach for screening military recruits for syphilis. His idea was that if the available assay performs well under a dilution of 1:k, then one can assay pools of specimens, each based on k persons, testing only individual specimens if their pool tested positive. To screen N persons in a population with a low prevalence, α, the number of assays one would need to conduct, on average, would be only

$$N \times \left[\frac{1}{K} + 1 - (1-\alpha)^{\kappa}\right].$$

In the study by Sankaranarayanan et al., α was approximately 0.10. Suppose an assay tolerates a dilution of 1:3 and the budget permits N assays. Pooling in groups of three would require (0.6)N assays, and the number of women who could be screened would be (1/0.6)N, or 1.67N. Further gains would accrue if women who presented for screening could be grouped according to risk, with individual-level assays reserved for high-risk women and pooling used for lower-risk women.

Clarice R. Weinberg, Ph.D.

National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709

1. Dorfman R. The detection of defective members of large populations. Ann Math Stat 1943;14:436-40.

THE AUTHORS REPLY: Suba et al., Ankit et al., and Cremer et al. call for more explanation regarding the lack of significant reductions in mortality from cervical cancer during the 8-year follow-up period after VIA screening or cytologic testing in our study. Although interstudy differences are not new, the discrepant results after VIA screening in the two randomized trials in India[1] have caused concern, especially in some countries that are beginning to implement VIA-based screen-and-treat programs.

The reasons for the discrepancies are not entirely clear to us. There were no differences in the follow-up care among the study groups. That HPV testing had a higher sensitivity for detecting potentially progressive precursor lesions than that of cytologic testing or VIA is clear from our findings. Nevertheless, long-term follow-up of the study cohorts may clarify the current lack of effect after VIA or cytologic testing. Perhaps the health education provided to the control women had an effect on the burden of cervical cancer, resulting in the absence of a significant detectable difference in the rate of advanced disease or deaths from cervical cancer between the control group and the VIA or cytologic-testing groups. An underestimation of the number of cervical-cancer cases and deaths in the control group cannot be ruled out either, since cervical cancers were diagnosed in the control group in women with symptoms who were seeking diagnostic services, and health services in the Osmanabad district are underdeveloped. Some women with disease might not have sought clinical care, and such cases and deaths might have been missed because of the lack of hospital records for such patients.

The above possibilities may account for the apparent lack of effectiveness of VIA and cytologic screening at this time. However, since we plan to continue the follow-up of the study groups for cervical-cancer incidence and mortality for several years, we will clarify the long-term effects of the interventions, including any delayed reductions in mortality in the cytologic-testing and VIA groups.

In reply to Mwanahamuntu et al. and Weinberg: approaches to the screening of women older than 30 years of age that involve using fewer rounds of screening with a highly sensitive test and targeting early diagnosis among women who are positive for high-risk HPV types are already good strategies to maximize the utilization of public health budgets. We hope that HPV testing will become affordable in all settings in the near future.

Rengaswamy Sankaranarayanan, M.D.

International Agency for Research on Cancer
69372 Lyon CEDEX 08, France
sankar@iarc.fr

Kasturi Jayant, M.Sc.

Nargis Dutt Memorial Cancer Hospital
Barshi 413 401, India

Surendra S. Shastri, M.D.

Tata Memorial Center
Mumbai 400 012, India

1. 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.