Indian J Med Res 135, May 2012, pp 576-579

Commentary

'See-and-treat' works for cervical cancer prevention: what about controlling the high burden in India?

Cervical cancer is a major public health problem in many developing countries and the absolute burden will increase in future if effective prevention measures are not undertaken. The global estimates for cervical cancer burden in the world around the year 2008 indicated that there were 5,30,232 new cases, 2,75,008 deaths, with four-fifths of the estimated global burden occurring in the low- and middle-income countries (LMICs) of South and South East Asia, sub-Saharan Africa, and South and Central America[1]. In this issue Singla and colleagues[2] report the results of a 'see-and-treat' approach combining visual screening with acetic acid (VIA)/Lugol's iodine (VILI), colposcopy and loop electrosurgical excision procedure (LEEP) in the context of a cervical cancer screening study in New Delhi, India.

'See-and-treat' electrosurgical loop excision of the cervical transformation zone is an excisional surgical procedure that enables simultaneous histologic diagnosis and treatment of cervical precancerous lesions, thus eliminating the need for a cervical punch biopsy and an additional visit. It involves two visits instead of the three visits [first a screening visit, a second visit for colposcopy and directed biopsy and the third visit for treatment of confirmed cervical intraepithelial neoplasia (CIN) cases] needed using Pap smear screening; however, it may be carried out in a single visit following VIA/VILI screening as the results of screening are immediately available facilitating immediate colposcopy and treatment with LEEP or cryotherapy.

The above approach should not be confused with a single visit 'screen-and-treat' when screen-positive women, without evidence of invasive cancer, are treated with cryotherapy or cold coagulation, without triaging procedures such as colposcopy and biopsy; 'screen-and-treat' eliminates investigations to confirm a diagnosis prior to treatment and minimises loss to follow up, delay in treatment and missed disease[3]. A major concern with 'screen-and-treat' cervical cancer prevention strategies is that a large number of women without precursor lesions will undergo cryotherapy/cold coagulation, although there are no data to suggest that overtreatment is harmful. On the other hand, it may provide some marginal benefit by protecting women against future HPV infection and by reducing cervical ectopy and targeting the transformation zone (TZ) where cervical neoplasia occur. Current evidence suggests that screen-and-treat interventions are safe, well accepted by women and effective in preventing cervical neoplasia[4,5]. Currently, Thailand is implementing a large 'screen-and-treat' programme with VIA and cryotherapy in 20 provinces and more than a million women have been screened with this approach[6].

Singla and colleagues[2] demonstrated the clinical utility, safety, and acceptability of "see-and-treat" approach using cross-sectional data in the Indian context and showed that the overtreatment associated with this approach was minimal, though the study sample size was rather small. 'See-and-treat' LEEP has already been used for treatment of 1141 women during 2000-2004 screened with VIA or cytology or HPV testing in the context of a population-based large randomized screening trial in Osmanabad district in Maharashtra in India[7] to maximize adherence to treatment and to minimise loss-to-follow up by reducing the number of visits, which has been the objective of the present study in New Delhi. In this study, all the women had satisfactory colposcopy and had a prior punch biopsy before LEEP; on the other hand, most women involved in the Osmanabad study had unsatisfactory colposcopy (51%) and had no prior punch biopsy (71%). The overtreatment rate in New Delhi study was 12.5 per cent where as it was 45 per cent in the Osmanabad study[7],

and these differences are likely due to the difference in the sources (hospital vs. general population) of screened women and sample sizes between the studies.

As discussed by Singla and colleagues[2], "see-and-treat" LEEP has been used in hospital-based health care settings in developed countries, in Latin American countries and China, involving women with cytologically high-grade squamous intraepithelial neoplasia (HSIL) referred to colposcopy clinics for further assessment and has been accepted as a useful option for the management of women with cytological HSIL[8-14]. The overtreatment was significantly higher when women with low-grade cytological abnormalities were included in 'see-and-treat' LEEP assessments[14]. In developed countries, selective use of 'see-and-treat' LEEP is practiced by experienced colposcopists who are able to reliably differentiate low-grade from high-grade disease by means of colposcopy; it is resorted to mostly if cytologic and colposcopic findings unequivocally indicate high-grade cervical intraepithelial neoplasia. On the other hand, the Indian studies[2,7] involved screen-positive women with all grades of precancerous lesions suspected at colposcopy. Thus, it is not surprising to see a high level of overtreatment reported in the Indian studies as compared to studies in developed countries.

Another novel 'see-and-treat' approach combined VIA, colposcopy and cryotherapy after directed punch biopsies in one or two visits in the treatment of women with colposcopic features of both high- and low-grade lesions in Osmanabad and Dindigul districts in India in the context of population-based randomized controlled screening trials[15,16]. These were large studies involving a total of 3581 women with colposcopically suspected lesions. Punch biopsies directed just prior to cryotherapy allowed the documentation of the histological nature of the lesions *a posteriori* after the treatment, and revealed that 40.3 per cent women did not have histologically confirmed CIN, indicating the level of overtreatment. 'See-and-treat' LEEP or cryotherapy were associated with a higher level of overtreatment, when women with features of suspected low-grade lesions were included, than studies involving those with suspected high-grade precancerous lesions[7,15,16]. However, as pointed out by Singla and colleagues, 'see-and-treat' with LEEP needs to be performed by doctors[2,7] as a higher skill level is needed for LEEP, whereas 'see-and-treat' with cryotherapy can effectively be carried out by nurses as shown in the southern Indian study[16].

Although it has been proposed that 'see-and-treat' LEEP may be considered as the work horse for the management of women with precancerous lesions in developing countries[17], this is feasible only in selected instances. A more pragmatic approach is 'screen-and-treat' cryotherapy, which is much more feasible and affordable, particularly when a large volume of screen positive women with CIN has to be managed[15,16].

It is worthwhile to consider the current status of cervical cancer in India, the country presenting the largest burden of disease in the world. One of every five cervical cancer patients in the world is an Indian woman[1]. In spite of this heavy burden and the important demonstration of feasible and cost-effective screening and treatment approaches for cervical cancer prevention in a number of well-conducted research studies in India, there has been very little scale-up of cervical cancer screening services in the country.

Despite the depressing statistics on cervical cancer, there is no government sponsored public health policy on prevention by either screening or vaccination or both in India. This large burden has not yet sufficiently seized the attention of public health authorities and there has been very little progress in publicly funded cervix cancer prevention initiatives. That significant progress could be made is clear from encouraging initiatives taken in countries such as Thailand, Bangladesh, Brazil, Argentina, and Mexico among others[18-22]. The situation is paradoxical given not only the large burden of disease but also that India has been responsible for some of the world-leading research demonstrating feasible and cost-effective approaches for cervical cancer screening and prevention in low- and medium-resource countries[23-32]. Randomized trials in India have shown a significant reduction in cervical cancer mortality following single round of screening with HPV testing[23] or VIA screening[24]. Studies from India have shown the safety, feasibility and efficacy of out-patient treatments for CIN[2,7,15,16,25]. These data from India have catalyzed both implementation and reorganization of national screening programmes in countries such as Argentina, Bangladesh, Morocco and Mexico among others, but little up-scaling of screening has happened in most States of India other than Gujarat, Maharashtra, Kerala, Tamil Nadu, Sikkim and West Bengal[33]. Bangladesh, for example, has established a VIA screening programme which uses both 'screen-and-treat' LEEP or cryotherapy for managing lesions, taking leads from the Indian studies[19]. Mexico is the first country in the world to establish primary testing with HPV followed by Pap smear triage as their national policy, based on their own research studies and

the outcome of research studies in India, Canada and Europe. They have already established a large network of high technology laboratories and have screened several million women with HPV tests. In Brazil more than 95 per cent of the municipalities provide Pap smear services and around 12 million smears are taken annually and the Brazilian Government has recently allocated an additional 2.4 billion USD for cervix and breast cancer screening over the next four years[34].

A further challenge to reducing the burden of cervical cancer in Indian women is the misinformation about the safety and efficacy of HPV vaccination as a control strategy, resulting in costly delays in resolving the controversies[35-37]. Meanwhile, neighbouring Bhutan introduced HPV vaccination as part of the national immunization programme. Malaysia, Panama, Mexico and Argentina are also implementing HPV vaccination of girls aged 10-13 yr either nationally or in selected provinces with high risk of disease. The time has arrived for India to take full advantage of the seminal research conducted on cervical cancer prevention in the country in order to tackle its own high burden of this disease and to prevent it. Cervical cancer predominantly affects socio-economically disadvantaged women; offering opportunities to reduce the suffering associated with this eminently preventable cancer is an ethical imperative that should go hand-in-hand with the remarkable economic progress the country is now achieving.

R. Sankaranarayanan
Section of Early Detection & Prevention
International Agency for Research
on Cancer, 150 cours Albert Thomas
69372 Lyon cedex 08, France
sankar@iarc.fr

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon: International Agency for Research on Cancer; 2010. Available from: *http://globocan.iarc.fr,* accessed on July 20, 2011.
2. Singla S, Mathur S, Kriplani A, Agarwal N, Garg P, Bhatla N. Single visit approach for management of cervical intraepithelial neoplasia by visual inspection & loop electrosurgical excision procedure. *Indian J Med Res* 2012; *135* : 614-20.
3. Gaffikin L, Blumenthal PD, Emerson M, Limpaphayom K. Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. *Lancet* 2003; *361* : 814-20.
4. Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC, Jr. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. *J Natl Cancer Inst* 2010; *102* : 1557-67.
5. Kuhn L, Wang C, Tsai WY, Wright TC, Denny L. Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. *AIDS* 2010; *24* : 2553-61.
6. Chumworathayi B, Blumenthal PD, Limpaphayom KK, Kamsa-Ard S, Wongsena M, Supaatakorn P. Effect of single-visit VIA and cryotherapy cervical cancer prevention program in Roi Et, Thailand: a preliminary report. *J Obstet Gynaecol Res* 2010; *36* : 79-85.
7. Sankaranarayanan R, Keshkar V, Kothari A, Kane S, Fayette JM, Shastri S. Effectiveness and safety of loop electrosurgical excision procedure for cervical neoplasia in rural India. *Int J Gynaecol Obstet* 2009; *104* : 95-9.
8. Santos C, Galdos R, Alvarez M, Velarde C, Barriga O, Dyer R, *et al*. One-session management of cervical intraepithelial neoplasia: A solution for developing countries. A prospective, randomized trial of LEEP versus laser excisional conization. *Gynecol Oncol* 1996; *61* : 11-5.
9. Ferenczy A, Choukroun D, Arseneau J. Loop electrosurgical excision procedure for squamous intraepithelial lesions of the cervix: advantages and potential pitfalls. *Obstet Gynecol* 1996; *87* : 332-7.
10. Ferris DG, Hainer BL, Pfenninger JL, Zuber TJ. 'See and treat' electrosurgical loop excision of the cervical transformation zone. *J Fam Pract* 1996; *42* : 253-7.
11. Numnum TM, Kirby TO, Leath CA, 3rd, Huh WK, Alvarez RD, Straughn JM, Jr. A prospective evaluation of "see and treat" in women with HSIL Pap smear results: is this an appropriate strategy? *J Low Genit Tract Dis* 2005; *9* : 2-6.
12. Li ZG, Qian DY, Cen JM, Chen GD, Shu YH. Three-step versus "see-and-treat" approach in women with high-grade squamous intraepithelial lesions in a low-resource country. *Int J Gynaecol Obstet* 2009; *106* : 202-5.
13. Kjellberg L, Tavelin B. 'See and treat' regime by LEEP conisation is a safe and time saving procedure among women with cytological high-grade squamous intraepithelial lesion. *Acta Obstet Gynecol Scand* 2007; *86* : 1140-4.
14. Cho H, Kim JH. Treatment of the patients with abnormal cervical cytology: a "see-and-treat" versus three-step strategy. *J Gynecol Oncol* 2009; *20* : 164-8.
15. Nene BM, Hiremath PS, Kane S, Fayette JM, Shastri SS, Sankaranarayanan R. Effectiveness, safety, and acceptability of cryotherapy by midwives for cervical intraepithelial neoplasia in Maharashtra, India. *Int J Gynaecol Obstet* 2008; *103* : 232-6.
16. Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, *et al*. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer* 2007; *96* : 738-43.
17. McAdam M, Sakita J, Tarivonda L, Pang J, Frazer IH. Evaluation of a cervical cancer screening program based on HPV testing and LLETZ excision in a low resource setting. *PLoS One* 2010; *5* : e13266.
18. Khuhaprema T, Attasara P, Srivatanakul P, Sangrajrang S, Muwonge R, Sauvaget C, *et al.* Organization and evolution

of organized cervical cytology screening in Thailand. *Int J Gynaecol Obstet* .In press 2012.

19. Nessa A, Hussain MA, Rahman JN, Rashid MH, Muwonge R, Sankaranarayanan R. Screening for cervical neoplasia in Bangladesh using visual inspection with acetic acid. *Int J Gynaecol Obstet* 2010; *111* : 115-8.
20. Arrossi S, Paolino M, Sankaranarayanan R. Challenges faced by cervical cancer prevention programs in developing countries: a situational analysis of program organization in Argentina. *Rev Panam Salud Publica* 2010; *28* : 249-57.
21. Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, Salmerón J, Uribe P, Velasco-Mondragón E, *et al*. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. *Lancet* 2011; *37* : 1868-73.
22. Lazcano-Ponce E, Lörincz AT, Salmerón J, Fernández I, Cruz A, Hernández P, *et al*. A pilot study of HPV DNA and cytology testing in 50,159 women in the routine Mexican Social Security Program. *Cancer Causes Control* 2010; *21* : 1693-700.
23. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, *et al*. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; *360* : 1385-94.
24. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, *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.
25. Rema P, Suchetha S, Thara S, Fayette JM, Wesley R, Sankaranarayanan R. Effectiveness and safety of loop electrosurgical excision procedure in a low-resource setting. *Int J Gynaecol Obstet* 2008; *103* : 105-10.
26. Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, *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.
27. Sankaranarayanan R, Thara S, Sharma A, Roy C, Shastri S, Mahe C, *et al*. Accuracy of conventional cytology: results from a multicentre screening study in India. *J Med Screen* 2004; *11* : 77-84.
28. Shastri SS, Dinshaw K, Amin G, Goswami S, Patil S, Chinoy R, *et al*. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bull World Health Organ* 2005; *83* : 186-94.
29. Nene B, Jayant K, Arrossi S, Shastri S, Budukh A, Hingmire S, *et al*. Determinants of womens participation in cervical cancer screening trial, Maharashtra, India. *Bull World Health Organ* 2007; *85* : 264-72.
30. Sahasrabuddhe VV, Bhosale RA, Kavatkar AN, Nagwanshi CA, Joshi SN, Jenkins CA, *et al*. Comparison of visual inspection with acetic acid (VIA) and cervical cytology to detect high grade cervical neoplasia among HIV-infected women in India. *Int J Cancer* 2012; *130* : 234-40.
31. Vedantham H, Silver MI, Kalpana B, Rekha C, Karuna BP, Vidyadhari K, *et al*. Determinants of VIA (Visual Inspection of the Cervix After Acetic Acid Application) positivity in cervical cancer screening of women in a peri-urban area in Andhra Pradesh, India. *Cancer Epidemiol Biomarkers Prev* 2010; *19* : 1373-80.
32. Sahasrabuddhe VV, Bhosale RA, Joshi SN, Kavatkar AN, Nagwanshi CA, Kelkar RS, *et al*. Prevalence and predictors of colposcopic-histopathologically confirmed cervical intraepithelial neoplasia in HIV-infected women in India. *PLoS One* 2010; *5* : e8634.
33. Sankaranarayanan R, Sauvaget C, Ramadas K, Ngoma T, Teguete I, Muwonge R, *et al*. Clinical trials of cancer screening in the developing world and their impact on cancer healthcare. *Ann Oncol* 2011; *22* (Suppl 7):vii20-vii28.
34. American Cancer Society. The Global Fight Against Cancer. Brazil Launches National Plan to Control Cervical and Breast Cancer. Available from: *http://cancer.blogs.com/international/2011/04/brazil-launches-national-plan-to-control-cervical-and-breast-cancer.html*, accessed on May 7, 2012.
35. Gupta H. New realities, new risks. The HPV vaccine should not be held hostage to middle-class fears and unease among medical professionals. February 14, 2011. The Indian Express 2011.
36. LaMontagne DS, Barge S, Le NT, Mugisha E, Penny ME, Gandhi S, *et al.* Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. *Bull World Health Organ* 2011; *89* : 821-30B.
37. Shetty P. Vaccine trial's ethics criticized. *Nature* 2011; *474* : 427-8.