Commentary on HPV screening for cervical cancer in rural India

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Abstract

In 2009 Sankaranarayanan et al published their findings from a large cluster-randomized, controlled trial of a single round of HPV testing, cytology testing or visual inspection with acetic acid - with appropriate treatment for those confirmed positive - as interventions to decrease mortality from cervical cancer. The control arm did not receive any screening or treatment. Several issues are brought up through the approval and conduct of this trial, which was carried out among high-risk women in rural Maharashtra, India. Specifically, this trial offers an opportunity to further discussion around clinical equipoise, identification of primary endpoints, observation of null effects, and the informed consent process, within the context of a low-income setting. Such discourse may shed light on the necessity and manner of examining a biomedical intervention in low-income settings, when the intervention is already considered efficacious in high-income settings.

Introduction

Sankaranarayanan et al make a convincing case for human papilloma virus (HPV) screening leading to reduced mortality from cervical cancer in a population of largely unscreened rural women in India (1). It is true that, as the authors say, "The most persuasive scientific evidence for the efficacy of a cancer screening test comes from RCTs with reduction in incidence of or mortality from the disease of interest as the end point."(2). Yet, in light of the controversy around the standard of care offered to research participants in low-income countries, the design of this study offers an opportunity to advance this debate. In particular, an in-depth discussion of the various concerns regarding the protection of human subjects may prove valuable. Such discourse may shed light on the necessity and manner of examining a biomedical intervention in low-income settings, when the intervention is already considered efficacious in high-income settings.

The study discussed here is a cluster-randomized, controlled trial of a single round of cervical cancer screening by either HPV testing, cytologic testing or visual inspection with acetic acid (VIA), starting in 1999 in rural Maharashtra, India. The primary outcome for the adult women enrolled (n=131,746) was cumulative mortality from cervical cancer. Women with positive screening results had confirmatory tests and appropriate treatment was provided when cervical precancerous lesions were found. Women in control villages did not receive any screening or treatment. Results indicated that, relative to women in the control group, women receiving HPV testing experienced a reduction in cervical cancer mortality. Reductions were not evident for women receiving cytologic testing or VIA.

Establishing equipoise

Established recommendations around screening programmes indicate that screening should be implemented only when there is - for the local population - an acceptable balance of false positive and false negative test results, and that screening programmes should lead to entry into efficacious treatment. For cervical cancer, the diagnostic capability of cytology has been established in a range of settings, as is the high cure rate from early detection of cervical precancer (3). It is for these reasons that cervical cancer screenings have been an established element of the standard of care in high-resource settings (4), making it controversial now to relax screening frequency recommendations; it is beyond question whether any screening is better than no screening. Furthermore, in 2001 Sankaranarayanan et al point out: "Frequently repeated cytology screening programmes - either organized or opportunistic - have led to a large decline in cervical cancer incidence and mortality in developed countries. In contrast, cervical cancer remains largely uncontrolled in high-risk developing countries because of ineffective or no screening."(5) (emphasis added)

By conducting this trial, the investigators and their ethics review boards necessarily imply that clinical equipoise exists. The investigators implicitly posit that the sensitivity of the various screening methods is not necessarily better than diagnosing cervical cancer by chance, and/or that the mortality for women testing positive by these methods and treated will not necessarily be lower than those who are unscreened but positive. After establishing that cervical cancer is a major source of mortality throughout India, clinical equipoise is possible only through a combination of these factors.

On a related point, it would be of interest to know whether the study was powered to detect a clinically relevant effect for India, or whether there was enough prior evidence that a single screening would reduce mortality by 50%. Future randomized controlled trials of this nature should provide further detail on the selection of parameters for the power calculation, as the clinically relevant effect to justify wide-scale implementation of a screening will differ by setting.

Endpoints and null effects

As Cuzick et al have stated, "Although some have argued that there is no direct evidence of the impact of cytology screening on cervical cancer, such as evidence from a randomised clinical trial, there are overwhelming and convincing epidemiologic data to infer the impact of successfully implemented cytology screening on reducing cervical cancer rates."(6) We may take note of Cuzick's endpoint, "cervical cancer rates", with

supportive evidence coming from papers published over the past three decades.

Indeed, it is of particular interest why cervical cancer mortality was a necessary endpoint; the authors themselves pointed out in 2005 that "The ultimate proof of efficacy of a screening test for cervical neoplasia is its ability to protect invasive cancer when implemented in a program setting."(2) A non-mortality endpoint has been found acceptable in another low-resource setting trial (7), and can be incorporated into a cluster-randomised design that allows investigators to estimate the measure of effect, while eventually providing participants with the known benefits of screening (8,9). Others have mathematically modelled screening interventions using well-established parameters of screening sensitivity, specificity, risk factor prevalence and natural history, which can provide compelling evidence of effect (10,11). It is questionable, then, whether human experimentation is required to demonstrate a mortality benefit from cervical cancer screening.

One of the most striking features of this trial is that while the statistically significant result from HPV screening is given ample discussion, the two null results (for cytology and VIA screening) are scarcely mentioned. In a 'gold standard' trial design - the RCT - all results from pre-specified hypotheses should be given equal consideration, as they were all subject to clinical equipoise at the trial's start. For cytology, some of the investigators involved with this study have earlier written that the evidence that cytology reduces cervical cancer mortality is "overwhelming and convincing" (6). And VIA is a screening method that has been widely adopted in other low-income countries. As such, it is incumbent on the investigators here to give equal attention to the result from these two arms' null results as they did for the significant HPV arm result. The authors initiated this process in response to letters to the New England Journal of Medicine (13). But to the extent that clinical equipoise existed prior to the trial, the null results do not appear to have provided any clarity to the effectiveness of cytology or VIA screening on cervical cancer mortality. This calls attention as to why there were cytology and VIA screening arms in the first place, and thus why the investigators subjected thousands of additional women to this research experiment.

Informed consent considerations

It is crucial to consider what consenting women understood with regards to the research question. While women in the intervention arms may not have completely understood the nature of their respective screenings, the unscreened women were unblinded to their study arm. How did the investigators communicate the potential and real risks and benefits of screenings vs no screening to these women?

Perhaps the investigators can provide additional detail on the education programme in the control arm, so that only 5.8% of these women "requested early detection at [Nargis Dutt Memorial Cancer Hospital] during the period 2000-2003 as a result of health education."(2) It is of interest to receive answers to a number of questions. First, what relationship did the health educators have to the investigators? Second, how did the consented women demonstrate comprehension of the educational programme? Third, to what extent were these women aware of the known benefits of cervical cancer screening, and the fact that they were selected into the study because they were part of a high-risk developing country population? These are all crucial elements of the informed consent process, and require special attention, given that 70-73% of the women had "no formal education".

Finally, while it is true that "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."(1), it is difficult to see how contamination of this intervention by study staff would be possible. If contamination would not be possible by staff, the investigators should identify how and why contamination would occur under an individual randomisation design. This is a critical aspect of intervention trial design; as cluster-randomisation increases the sample size needed to detect a given effect, relative to individual randomisation, the exact source of the contamination should be identified so as to inform future screening trials.

Conclusion

It is important to note that Sankaranarayanan's co-investigators are largely locally based and the study itself received approval from international and Indian national ethics committees. However, a discussion around these issues will be highly informative. There are numerous demonstrably effective routine screening programmes in high-income settings that detect conditions with significant burden in low-resource settings. It is incumbent on the public health community to establish whether randomised control trials are required to justify their implementation in the latter, and the informed consent process and standard of care used for a control group.

References

1. 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. HPV Screening for cervical cancer in rural India. *N Engl J Med.* 2009 Apr 2;360(14):1385-94.
2. Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, Malvi SG, Chinoy R, Kelkar R, Budukh AM, Keskar V, Rajeshwarker R, Muwonge R, Kane S, Parkin DM, Chauhan MK, Desai S, Fontaniere B, Frappart L, Kothari A, Lucas E, Panse N; Osmanabad District Cervical Screening Study Group. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer*. 2005 Sep 10;116(4):617-23.
3. World Health Organization. *Comprehensive cervical cancer control: a guide to essential practice*. Geneva: World Health Organization; 2006.
4. US Preventive Services Task Force. *Screening: cervical cancer* [Internet]. 2003 [cited 2010 Oct 8]; Available from: http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm
5. Sankaranarayanan R, Budukh AM, Rajkumar R. Effective screening programmes for cervical cancer in low-and middle-income developing countries. *Bull World Health Organ*. 2001;79 (10):954-62.
6 Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, Dillner J, Meijer CJ. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine*. 2008 Aug 19;26 Suppl 10:K29-41.

7. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*. 2005 Nov 2;294(17):2173-81.
8. Bonell CP, Hargreaves J, Cousens S, Ross D, Hayes R, Petticrew M, Kirkwood BR. Alternatives to randomisation in the evaluation of public health interventions: design challenges and solutions. *J Epidemiol Community Health*. 2010 Jul; 65(7): 582-7.
9. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007 Feb;28(2):182-91.
10. Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA*. 2001 Jun 27;285(24):3107-15.
11. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahe C, Wright TC; Alliance for Cervical Cancer Prevention Cost Working Group. Cost-effectiveness of cervical-cancer screening in five developing countries. *New Engl J Med*. 2005 Nov 17;353(20):2158-68.
12. Foltz AM, Kelsey JL. The annual Pap test: a dubious policy success. *Milbank Mem Fund Q Health Soc*. 1978 Fall;56(4):426-62.
13. Sankaranarayanan R, Jayant K, Shastri SS. Authors' response: HPV screening for cervical cancer in rural India. *New Engl J Med*. 2009;361(3):306.

Acknowledgments and funding: *The author thanks Reena Gupta, Caitlin Gerdts, Douglas Heimburger and Sten Vermund for their thoughtful comments and suggestions. This work was supported by the United States National Institutes of Health Fogarty International Center, through the International Clinical Research Fellows Program at Vanderbilt University (R24TW007988) and the American Relief and Recovery Act. The views presented herein are solely the responsibility of the author and do not necessarily represent the official position of the funders or those acknowledged.*

Reply to S D Rathod's Commentary on HPV screening for cervical cancer in rural India

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The study in Osmanabad district, India (1), was organised to measure the effect of a single round of screening by HPV testing, or quality assured cytology, or visual inspection with acetic acid (VIA) on cervical cancer incidence and mortality, whereas reductions in disease have followed repeated rounds of high-intensity screening in developed countries. Prior to this study there was only evidence from model-based studies that a single round of screening may lead to significant reductions in disease burden. Thus, in contrast to the impression given by Rathod (2), this study was not a repeat of work conducted in developed countries but was unique in addressing the impact of a single round screening with different tests, with a research question and study design directly relevant to developing countries. It is crucial that this type of high-quality research is encouraged in order to inform public health decisions in regions where health services face difficult challenges.

The study was designed as a cluster randomised trial to avoid contamination between the study groups and for logistic convenience. We decided that providing services to clusters of women with a given screening test is more convenient in terms of clinic organisation than providing different screening tests in the same village clinic for a group of women based on individual randomisation. Moreover, it prevents any possible unintended error in providing appropriate screening test as per randomisation and women crossing over to different interventions at random.

The standard of care for cervical cancer control in India is clinical diagnosis and treatment of invasive cancer only when symptomatic women seek medical attention. There is no organised or large-scale opportunistic cervical cancer screening programme anywhere in the country. Around one million cervical smears are taken annually in a sporadic fashion, mostly in urban areas, in a country where there are more than 150 million women in the age group 30 to 59 years. For instance, only 8 of the 131,746 women aged between 30 and 60 years in our study population had ever had a Pap smear, indicating the scarcity of routine screening in the general population.

Whenever a new intervention is evaluated, it is compared with the standard of care existing in the country. It is important to know if a single round of screening has the ability to reduce disease burden significantly, over and above the existing care, before taking decisions on implementing them as a public health policy, particularly in poorly financed health services. Thus the control group in our study was not offered screening, but they were educated on a person to person basis on cervical cancer, its risk factors, symptoms and signs, its prevention, early detection, treatment and where to seek cytology and follow-up services, by the study health workers who interviewed them for socio-demographic factors. Probably due to the education received, 1,946 (6.2%) women in our control group sought Pap smear and among those 15 were detected with histologically proved high-grade disease, 41 were diagnosed with invasive cancer, and all were offered appropriate treatment.