Prospects of Cervical Screening in Developing Countries

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**Dr. Lynette Denny:** “Good-morning. I’d like to thank the Organizing Committee for inviting me to present to you today on the prospects for cervical cancer prevention in developing countries. I’d also like to acknowledge my collaborators Dr. Kuhn, Dr. Pollack, Dr. Thomas Wright, as well as AVSC International and the Bill and Melissa Gates Foundation who have funded this work. Although there are no randomized control trials, data from case controls and cohort studies strongly suggest that both the incidence of and the mortality from cervical cancer can be reduced by mass organized cervical cancer screening programs. The majority of women who develop cervical cancer have either never been screened, have a long screening interval, have been inappropriately managed, or in fact, there has been false negative cytology. In contrast to many countries in the developed world where organized screening programs have in fact rendered cervical cancer a relatively rare disease, there are no organized screening programs in most of the developing world where the incidence of this cancer is the highest. In those African countries where cancer registries exist, the incidence of cervical cancer is estimated to range between 39 per 100,000 women in South Africa to 67 per 100,000 women in Zimbabwe, and this data probably underestimates the true incidence due to underreporting.

In 1985, as was pointed out by Dr. Nazeer, the WHO estimated that less than 5% of women in the developing world had been screened and there’s little reason to doubt that this has changed. There are many complex reasons as to why screening has not been established in poor countries but the situation in sub-Sahara in Africa is illuminating. For instance, the estimated per capita expenditure per year on health is around $10, much less than many countries, and this is compared to $4,000 per person in the United States. Their competing health needs with an average maternal mortality ratio of 650 per 100,000 women not to mention the pandemics of malaria, tuberculosis, and more recently HIV. Their limited human and financial resources with an average physician to patient ratio of 1 to 24,000 is reaching up to 1 to 75,000 in some countries. War and civil strife are endemic in many African countries with often devastating consequences for health. For instance, it is estimated that in the Rwanda genocide, 30% of the health personnel of that country were murdered. There is also widespread poverty with only 25% of sub-Sahara and African people having access to safe water and sanitation. While these factors are perhaps the most important variants, establishing organized screening programs, the nature of the traditional screening test of cervical cytology poses an additional barrier.

Cervical cytology requires a relatively sophisticated laboratory infrastructure with functioning referral systems. The results if delayed would be cause of a notoriously high default rate in developing countries. Cervical cytology also has very poor reproducibility unless subjected to stringent quality control and ongoing training of cytotechnicians and pathologists. Colposcopy represents another barrier. Colposcopic services are not available in most parts of sub-Sahara in Africa, and where they do exist, they tend to be located in urban tertiary institutions inaccessible to the majority of apterous women. Ideally, if we’re to consider alternative methods of cervical cancer prevention, we need to think about the following criteria. The whole process of screening, diagnosis, treatment, and follow-up needs to be provided at the primary healthcare level by primary healthcare workers, preferably nurses as opposed to doctors who are in far shorter supply. We need to minimize repeat visits to the clinic and eliminate the necessity for colposcopic triage. We need to be using low technology screening tests and low technology methods of treatment that can be provided on site. We need a rapid turn around of results, if not immediately, certainly within days of screening. Finally, any alternative to the tried and tested method of cervical cancer prevention that
is cytology followed by colposcopy, histological sampling, and treatment needs to be proved to be as effective and certainly as safe. Direct visual inspection of the cervix offers one alternative also known as VIA. This process requires training a nurse to pass a speculum, to visualize the cervix, to wash out with 5% acidic acid, and to determine whether there is an acetowhite lesion. It provides an immediate on site results, it’s a low technology test, the equipment requirements are limited, and certainly there is good data as it just has been shown by the first speaker that the sensitivity is at least equivalent to cytology.

HPV DNA testing is another alternative, the current technology for testing is advanced and it’s commercially available. The tests are robust, they’re reproducible, and they’re objective. Results are available within hours, large numbers of tests can be performed per day, it has a very, very low false negative rate, and while the current testing is prohibitively expensive and complex for developing countries, we need to think ahead and realize that this test could become as simple as a side room test or certainly a test that could be performed at district level so we need to prepare for when this technology can become more accessible. To look at the test performances of these different screening tests, we began the Cape Town Study in January of 1996 where we recruited 2,944 women who were previously unscreened and age 35-65 years of age. These women were recruited from a squatter camp twenty kilometers outside Cape Town. All women were screened with a Pap smear, defined positive, low cell, high cell, or cancer. They were screened with HPV DNA testing using Hybrid Capture I, which has probes to detect nine high-risk types of HPV. We used a high cut-off for referral to colposcopy as it is a quantitative test and that’s with ten times the positive control. In addition, we re-tested a subset of women with histologically confirmed low cell, high cell in cancer, and a random sample of 243 women with no evidence of disease with a new generation Hybrid Capture II which has probes to detect thirteen high risk types of HPV. All women were screened with direct vision inspection either with the naked eye or with a 2.5 times handheld magnifying lens and cervicography.

These were some of the results, as you can see the majority of women were in the 35-39 age group with 16% of women who were over the age of 50. What is interesting is that the prevalence of HPV DNA, and this is high risk HPV DNA, did not decrease with age and was equivalent in the 60-65 age group as the 35-39 age group. Fourteen percent of the women had no education and were illiterate and only 3% of women had achieved high school graduation. There was no difference in the prevalence of HPV DNA according to educational status. DVI identified 18% of the women as having a positive test. HPV DNA testing using the higher threshold identified 6%, when the threshold was reduced to one times the positive control, it identified 16% of the women as positive, and cytology identified 8%. This slide shows, for example, that all the women who were DVI positive received their results immediately, and 96% of these women underwent colposcopy. HPV DNA results were available within 2-6 days of women being screened, and 95% of these women underwent colposcopy. Cytology results were available two weeks later, only 86% of these women underwent colposcopy suggesting that the longer the time between being screened and receiving results the greater the default rate. These give the sensitivity and specificities of the different tests. Cytology and HPV DNA testing at the lower threshold for a positive test had equivalent sensitivity. DVI had only a marginally lower sensitivity than those two tests but with a significantly lower specificity at 84%. Increasing the threshold for a positive HPV test reduced sensitivity but increased specificity to be equivalent to that of cytology. Of those women who were DVI positive, only 11% in fact had high cellular cancer but what is important in this slide is that all four tests had extremely high negative predictive values suggesting that women with a negative test were extremely unlikely to harbor undetected disease.

Now if we were to screen women with DVI and offer them immediate treatment what would the outcome be? DVI will identify 1 in 5 women as having a positive test requiring treatment, however, it will identify two-thirds of the cases of high cell in cancer in the screened population but 80% of women undergoing treatment would not have cervical disease. Is there a method of improving this? We extrapolated our data into a concept called two-stage or sequential screening; that is if your resources are large you screen your entire population with DVI and only select those for a second screening test such as a Pap smear or a HPV test. Only if both tests are positive would you refer the patient for treatment. The result of this is that you’d dramatically reduce the number of women referred for treatment from 18% to 3%-4%. There’s a significant drop in sensitivity to less than 50% but a dramatic increase in specificity. In some low resource centers this may be acceptable. The low specificity of DVI may relate to the fact that there’s a lack of standardized training methods and definitions of what are significant acetowhite lesions. In addition, there’s a very high prevalence of low genital tract infection among poor women. For instance, our nursing
sister noted that 84% of the women she screened had significant vaginal discharge. In phase 2 of this study in which we’ve recruited a further 3,000 women from the same population, 20% of women had culture proven trichomonas infection, 6% had gonorrheal chlamydia infection of the cervix, and 8% were HIV positive. Remember, these are women age 35-65 years of age. Looking at HPV DNA testing in a little more detail using the Hybrid Capture I, what we see here is that with increasing severity of disease so does the prevalence of HPV DNA increase. In addition, by changing the threshold for a positive test, the false positive rate can be dramatically reduced. These results were replicated using Hybrid Capture II except in this case, 100% of cancers were identified and 87% of the cases of high cell. On the down side, the number of women at low risk for disease was increased to 18%. In the second phase of our study, in addition to the clinician-taken sample for HPV DNA testing, women inserted a Dacron swab into the vagina themselves for further HPV testing. What is interesting here is that while the clinician- taken sample before and by far is the best, the sensitivity of self-testing for high cell and for cancer was higher if not equivalent to cytology, and this certainly offers a whole new method and a whole new approach to screening. HPV DNA testing is standardized, it’s objective, and mid-level technicians can test large samples each day compared to cytology, which requires highly trained cytotechnicians who can evaluate only 60-80 samples per day. The sensitivity of HPV DNA testing whether it’s self-sampling or clinician-taken sampling is at least as good as cytology and in most instances much better. The specificity can be altered by changing the threshold that one uses to define a positive test and this needs further work. Furthermore, HPV DNA negative women are at extremely low risk for undetected high cell in cancer and need very little surveillance. In addition, HPV DNA testing identifies those women who are at high risk for developing high cell or cancer in the future. Our study has certainly shown the potential utility of HPV DNA testing as a primary screening test. However, there are some unanswered questions, for example, would it be acceptable for large numbers of women to know that they’re being tested for a recognized sexually transmitted disease? What will this do to compliance and what would this do to acceptability? What would be the safety and efficacy profile of treating women simply on the basis of a positive HPV DNA test knowing that a significant number of women would not in fact have cervical disease? It may well be that this is not a bad thing to do. It may well be that it is worth the sacrifice to over treat large numbers of women to prevent cancer in a few. To evaluate this we are currently conducting a randomized prospective trial of screening and treating women with DVI and HPV. We hope to have some data on this in a year or two. The other point is can the laboratory requirements of HPV DNA testing be reduced so that this can be performed at district level? This is critical, in its current format, I doubt it can ever be used in developing countries. Finally, we have to ask what will be the impact of the HIV epidemic on the utility of HPV DNA testing as a primary screening test? Thank you very much for your attention.”

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