EDITORIALS

# From India to the World — A Better Way to Prevent Cervical Cancer

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In this issue of the *Journal*, Sankaranarayanan et al.[1] report the results of a randomized clinical trial of screening for cervical cancer involving more than 130,000 women in India. The authors conclusively showed that a single round of screening for human papillomavirus (HPV) dramatically reduced the incidence of advanced cervical cancer and cervical-cancer mortality within 8 years far more than a single conventional cytologic test or visual inspection of the cervix with acetic acid (VIA).

The implications of the findings of this trial are immediate and global: international experts in cervical-cancer prevention should now adapt HPV testing for widespread implementation. Low-resource countries do not need to establish large cytologic-testing (Papanicolaou) programs whose effectiveness requires repeated screening. VIA that is performed by health workers, the least expensive but least accurate option, may reduce mortality slightly.[2]

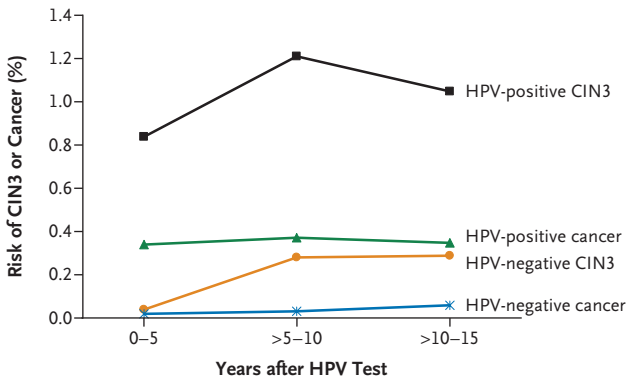
Very few screenings of any kind will be possible during a woman's lifetime in most low-resource regions, where 80% of the half-million global cases of cervical cancer occur every year. Screening for HPV or its related cytologic and visual changes is not cost-effective among women at a young age because HPV is a common sexually transmitted agent in young women and new infections typically resolve. However, among Indian women between the ages of 30 and 59 years, the investigators observed substantial differences in risk between women who tested positive and those who tested negative on single screening for HPV.

Knowledge of the natural history of HPV suggests that the time since first intercourse is the logical time scale for program planning.[3] A single HPV test that is performed 15 to 20 years after the median age of first sexual intercourse will detect many easily treatable, persistent infections and precancers while limiting overtreatment.[4]

The well-publicized efficacy of newly approved prophylactic HPV vaccines against HPV type 16 (HPV-16) and HPV type 18 (HPV-18)[5] does not diminish the importance of HPV screening. Even when HPV vaccines are affordable and widely used, they will not substantially decrease rates of cervical cancer for decades because of the long latency between infection and cancer.[3] As the Indian trial shows, screening for HPV can lower the rate of death from cervical cancer within 5 to 10 years. Optimally, next-generation HPV vaccines will soon provide coverage for additional carcinogenic HPV types, and fewer doses of the vaccine will be required. When such vaccines become available, it would be ideal to vaccinate girls and screen their mothers for one generation.

What is stopping widespread implementation of HPV screening? In low-resource countries, we need to define regional, age-specific HPV prevalence patterns; validate low-cost, simple, and accurate HPV tests; and develop an infrastructure aimed at the treatment of HPV-positive women.

Knowing HPV prevalence patterns according to age is essential for planning a cost-effective screening program. HPV screening worked in the Indian trial because only 10% of women were found to be HPV-positive. Although age-specific HPV prevalence in women over the age of 30 years generally declines from a peak at younger ages, the prevalence remains consistently above 20% in some low-resource regions.[6] At this prevalence




| No. at Risk | | | |
|---|---|---|---|
| HPV-positive | 2,388 | 1,076 | 858 |
| HPV-negative | 15,452 | 8,777 | 7,134 |

**Figure 1. Absolute Risk of Invasive Cervical Cancer or Cervical Intraepithelial Neoplasia Grade 3 (CIN3) during Three 5-Year Intervals after a Single HPV Test.**

Data are shown for more than 17,000 women who were enrolled in the Kaiser Permanente Health Plan in Portland, Oregon, in 1989 and 1990 and who were followed passively for approximately 16 years as they returned for routine cytologic screening.[11] The numbers of women who were screened by cytologic analysis at least once during each of the three 5-year follow-up intervals are shown under the graph, according to their human papillomavirus (HPV) status at baseline; colposcopically guided biopsy was generally recommended for women with atypical cells of undetermined significance or worse. Testing with a single Hybrid Capture II (Qiagen) assay (which was used by Sankaranarayanan et al.[1]) did not affect referral and resultant disease ascertainment and provided substantial risk stratification over a prolonged period, unlike the results of cytologic analysis (data not shown). In a comparison of HPV-positive women with HPV-negative women, the risk ratios for CIN3 were 21.0 in the first 5-year interval, 4.3 during the 5-to-10-year interval, and 3.6 during the 10-to-15-year interval. The risk ratios for invasive cancer during the same time intervals were 17.0, 12.3, and 5.8, respectively.

level, too many women must undergo triage or treatment for a screening program to be practical without a more specific assay. Determining the cause of the high prevalence of HPV DNA in older women and the use of alternative HPV-based biomarkers (testing for HPV-16 and other highest-risk HPV types and measuring p16 or viral E6 expression) might permit cost-effective programs of risk stratification in these regions, if suitable assays can be developed.

Affordable and accurate HPV DNA testing is already a reality. A simple, highly sensitive, low-cost test[7] is being used in demonstration projects in several countries. The search for even simpler and less expensive tests should continue.

The extended protection afforded by a single round of HPV testing will permit screening programs that have minimal infrastructure. In some regions, colposcopy and biopsy of suspicious lesions in HPV-positive women (procedures that were used in the Indian trial) might be removed from the prevention program to create "screen-and-treat" protocols, minimizing cost and loss to follow-up. VIA might be used as a triage step in HPV-positive women but only to rule out obvious cancers and other disorders that cannot be treated by cryotherapy. However, the quality of widely available cryotherapy might not be adequate to fulfill the promise of HPV screening. The development of optimal outpatient treatment for HPV-positive women in low-resource settings, including those with precancerous changes, should be a major priority.

Because persistent HPV infection is the main cause of cervical cancer everywhere, the trial in India will influence screening programs in cost-conscious developed countries. Complementing the Indian trial's assessment of cancer mortality, trials in Europe and North America recently showed that HPV screening is much more sensitive than cytologic testing for the detection of precancerous conditions.[8-10] Moreover, we found in a nonrandomized, prospective study that the stratification of women according to the risk of precancer and cancer on the basis of a single HPV test extends well beyond 10 years (Fig. 1).[11]

In developed nations, HPV testing at extended screening intervals could eventually replace repeated cytologic testing as the primary screening method. Cytologic testing might be used to stratify risk further by identifying HPV-positive women at highest risk for cancer.[12] In these countries, a widespread transition from a good method (frequent cytologic testing) to a better one (less frequent HPV screening) will require high-quality testing that is widely available and properly priced, the establishment of correct screening intervals and related health messages, and the promulgation of clinical guidelines and reimbursement policies to avoid overtreatment of benign infections.

In the United States, switching to primary HPV screening will be contentious, partly because lengthening the interval between cervical screenings seriously disrupts established gynecologic clinical practice. The avoidance of overtreatment will be crucial. Doctors and patients must realize that at any age, recent-onset HPV infection should be considered benign and that knowing that a woman is HPV-positive soon after first intercourse is not useful.[13] HPV negativity should lead to less

intervention, because it provides important reassurance that the screening interval can be lengthened safely. Notably, Sankaranarayanan et al. found no cancer deaths among HPV-negative women in the HPV-testing group during an 8-year period. The remarkable promise of the Indian trial presents a worthy global challenge to implement smart, regionally tailored strategies that will efficiently save millions of lives in the years ahead.

Dr. Schiffman reports being a medical monitor of a trial of prophylactic HPV vaccination sponsored by the National Cancer Institute (NCI); and Dr. Wacholder, serving as the statistician for the same NCI-sponsored HPV vaccination trial. No other potential conflict of interest relevant to this article was reported.

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# Sunset for Statins after AURORA?

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Reducing mortality from cardiovascular disease among patients undergoing dialysis is a global public health challenge. The past 10 years have seen trials of many interventions designed to improve survival and cardiovascular outcomes in these patients.[1-4] Unfortunately, none of these interventions have been shown to be effective, despite beneficial effects in surrogate markers.[5,6] It appears that statins have now joined this group of "promising but ineffective" interventions.

In this issue of the *Journal*, Fellström et al.[7] report on the results of A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA). There were no significant effects of rosuvastatin, at a dose of 10 mg per day, in 2776 patients undergoing hemodialysis, either on a composite end point (hazard ratio for the combined end point in the rosuvastatin group, 0.96; 95% confidence interval [CI], 0.84 to 1.11) or on its single components. Yet rosuvastatin lowered low-density lipoprotein (LDL) cholesterol levels significantly and with a magnitude that the researchers had predicted. Given the consistent benefits of statins shown in many large trials involving other patients,[8] the obvious question is why the same benefit was not shown in AURORA.

First, the study may not have had sufficient statistical power. Event rates in the placebo group in AURORA were lower than expected (9.5%, vs. 11.0% anticipated). The basis of the calculation of the sample size was a postulated 25% reduction in event rates, which is consistent with the observed linear relationship between the magnitude of LDL cholesterol lowering with statin therapy as compared with placebo observed in AURORA and the proportional reduction in cardiovascular events in other trials.[8] The lower bound of the 95% confidence interval for the primary end point was 0.84; hence, the results of AURORA are consistent with a relative reduction in major cardiovascular events of up to 16%, which (with absolute