



## The Promise of Global Cervical-Cancer Prevention

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Cytologic screening has significantly reduced the rates of cervical cancer in many developed countries. However, cervical cancer remains a leading form of cancer among women living in low-resource

regions of the world (see map) and often kills women at young ages, when they are still raising families. In these same regions, programs to prevent cervical cancer are unavailable or underfunded because they compete with many other priorities.

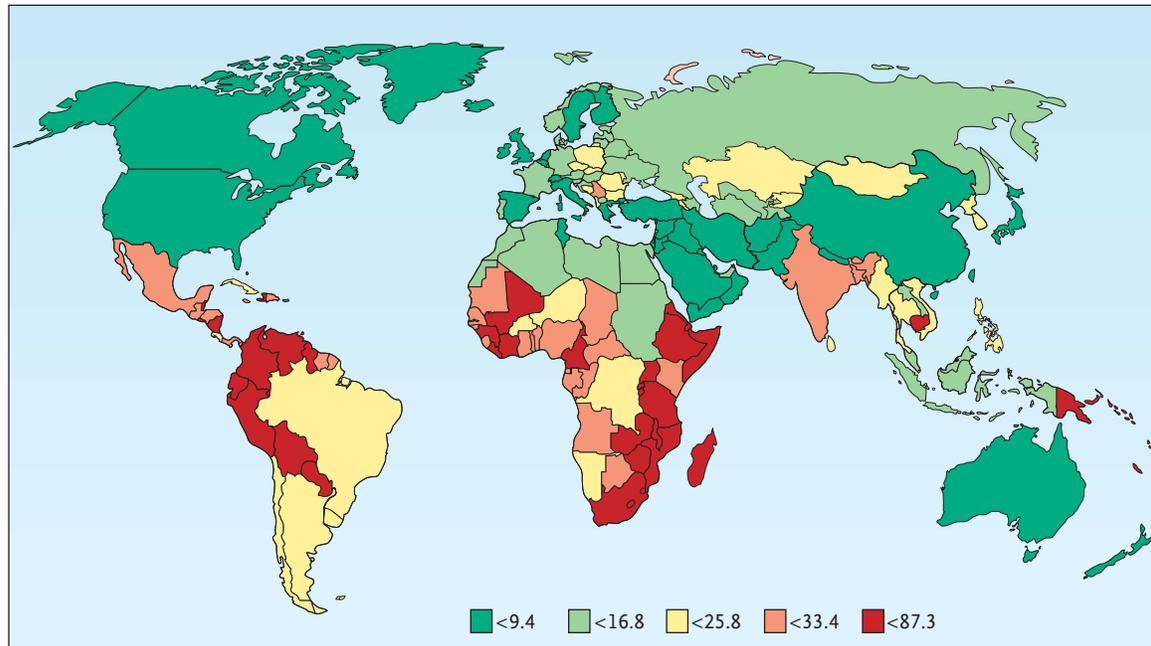
The current standard of cervical-cancer prevention requires three clinical visits: one for screening, one for a colposcopically guided (i.e., magnified) biopsy for women with abnormal screening results, and one for treatment of precancerous conditions. Single cytologic screenings are insensitive and do not provide sustained reassurance with regard to the risk of cancer. Program effectiveness is achieved

by repeated iterations of the three-visit cycle, but such repeated testing is usually unachievable in resource-limited regions. Fortunately, as discussed by Goldie et al. in this issue of the *Journal* (pages 2158–2168), new practical options for cervical-cancer prevention are becoming available.

Promising new prevention strategies are based on our improved knowledge of the pathogenesis of cervical cancer. Persistent cervical infection with 1 of approximately 15 types of human papillomavirus (HPV) causes virtually all cases of cervical cancer<sup>1</sup> as well as the preceding changes, which are evident on cytologic, histologic, and visual examination. Because there is a single,

root cause of cervical cancer, we can envision both primary prevention through vaccination against HPV in young women and secondary preventive screening directly for carcinogenic HPV in older women (see diagram).

HPV DNA testing is more sensitive and the results more easily reproducible than cytologic screening and colposcopy for the detection of existent and incipient cervical precancerous conditions and cancer. As a corollary of the high sensitivity of HPV testing, a negative test for carcinogenic HPV types provides a degree and duration of reassurance not achievable by any other diagnostic method. By understanding the natural history of the carcinogenic HPV types in relation to stages of development of cervical cancer, we can now adjust screening to meet resources. We can target the optimal age at which screening should be performed and deter-



#### Incidence of Cervical Cancer Worldwide.

Numbers indicate cases per 100,000 population.

mine the most cost-effective testing intervals, screening tests (e.g., the number of HPV types that range from strongly to weakly carcinogenic that should be included in an assay), and thresholds for test positivity (very low viral loads only minimally elevate the risk of precancerous conditions and cancer).

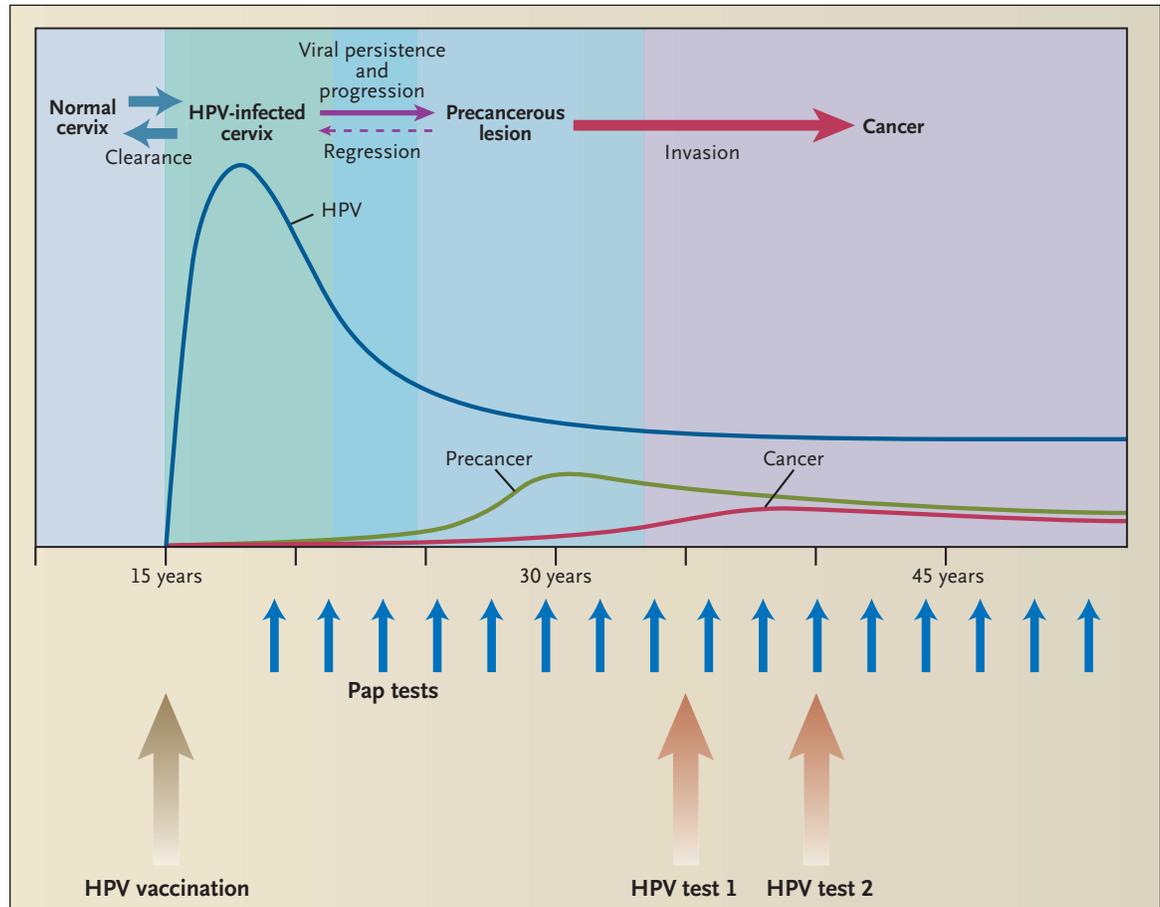
As appropriately modeled by Goldie et al., in low-resource regions, screening should be focused on reaching women at the time of the peak risk of treatable precancerous conditions due to persistent infection and before the average age at which incurable invasive cancers occur (see diagram). In the several settings the authors analyzed, they found that screening women once, at 35 years of age, or twice, at 35 and 40 years, with current HPV DNA tests targeting 13 carcinogenic types at conventional thresholds of viral detection can

achieve more cost-effective reductions in cancer than can conventional cytologic methods because of the greater accuracy of HPV DNA tests. Conversely, it is not necessary to detect transient HPV infection or the associated mild pathological or visible epithelial abnormalities in young women, among whom acute and resolving HPV infections are extremely common in the decade after the initiation of sexual activity. In fact on the basis of what we now know, cervical-cancer screening programs in resource-poor settings should purposely be separated from clinical services that primarily serve young women.

Each round of prevention must be compressed into the fewest number of visits to reduce costs and loss to follow-up. In terms of screening, three-visit strategies or even two-visit strategies (in which women with abnormal screening results are called back and treat-

ed without a confirmatory colposcopic biopsy) are not optimal choices in low-resource settings. HPV DNA tests are now being developed into rapid, robust, easy-to-use formats. When these HPV tests are available, one-visit “screen-and-treat” strategies will be very appealing. Women who have negative HPV tests can be viewed as having a low risk and can be discharged. Women with positive HPV results can undergo further assessment through visualization of the cervix to determine the appropriate management strategy; most women in this setting can be treated with cryotherapy, which is widely available and easy to perform on site. Only women with severe or extensive precancerous conditions or obvious cancer that is untreatable by cryotherapy will require referral to a hospital for expert gynecologic management.

To complete the screen-and-



#### The Natural History of HPV Infection and Cervical Cancer.

The peak prevalence of transient infections with carcinogenic types of HPV (blue line) occurs among women during their teens and 20s, after the initiation of sexual activity. The peak prevalence of cervical precancerous conditions occurs approximately 10 years later (green line) and the peak prevalence of invasive cancers at 40 to 50 years of age (red line). (The peaks of the curves are not drawn to scale.) The conventional model of cervical-cancer prevention is based on repeated rounds of cytologic examination, including Papanicolaou smears, and colposcopy (small blue arrows). Alternative strategies include HPV vaccination of adolescents (large beige arrow), one or two rounds of HPV screening at the peak ages of treatable precancerous conditions and early cancer (large reddish-brown arrows), or both.

treat strategies, we urgently need to validate a treatment that is inexpensive, safe, reliably effective, and similar in performance to cryotherapy with nitrous oxide, which is not widely available. Cryotherapy with carbon dioxide is inexpensive and ubiquitous but is not dependable in terms of performance. Improving an inexpensive kind of cryotherapy or finding an alternative for use in low-resource settings is a critical missing link that will translate

improved screening into improved prevention.

Promising vaccines designed to prevent infection with HPV types 16 and 18 have been shown to have very high efficacy against new, persistent infections with these major carcinogenic types (which account for 70 percent of cancer risk).<sup>2,3</sup> Because these vaccines are not designed to treat infection once it occurs, young women would need to be vaccinated to achieve maximal effect.

Vaccine evaluations are still under way. The follow-up data from these trials will establish the relative roles of HPV vaccination in young women and of screening in older women. As is true for the requirements for screening, HPV vaccines will need to be adapted for low-resource settings (i.e., they will have to be low-cost and single-dose immunizations). Ultimately, programs to prevent cervical cancer may integrate these complementary approaches

— vaccination in young women and screening in older women — if they are proved to be cost-effective.

Inevitably, the estimates used by Goldie et al. will be challenged by groups concerned about the conclusions or assumptions regarding costs, prevalence, test performance, and other details of the base-case and sensitivity analyses. For example, the analysis by Goldie and colleagues suggests that visual inspection of the cervix with acetic acid might be an effective alternative to other types of screening. However, the degree of accuracy achievable with visual assessment performed

alone can be quite variable, which shows that the best prevention strategies should be determined regionally on the basis of local competencies, costs, needs, and perhaps most important, acceptability.

The important conclusion is that within a few years, we expect to have multiple tools not only to improve cervical-cancer screening, but also to restrict the spread of its viral cause. Because it is feasible to prevent cervical cancer and to avert the suffering it causes so many women and their families, cervical cancer deserves to be a high priority among global efforts to prevent cancer.

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## Genetic Diversity in Melanoma

Paul S. Meltzer, M.D., Ph.D.

As with other cancers, the process of the transformation of normal melanocytes into malignant melanoma requires the acquisition of genomic abnormalities. Although progress in the search for the targets of genetic aberration in cancer has been stunning in many respects, the clinical effect of this work has been limited. But it is clear that tracking down the genetic changes in cancer is no mere academic exercise; rather, it has proved to be a powerful approach to the selection of therapeutic targets. Progress in the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumor, and some lung cancers can be directly linked to the development of therapies that target specific pathways activated by acquired somatic mutations. The pursuit of genetic abnormalities in can-

cer has taken on new excitement and urgency with the realization that their identification may dramatically improve therapeutic options for patients with the disease. The challenge remains to connect specific genetic targets to specific cancers — a task made more daunting by the large number of genes and the heterogeneity of cancers.

There had been little cause for excitement about the development of targeted therapeutics for melanoma until the discovery that a high proportion of melanomas have activating mutations in the gene encoding the signaling molecule BRAF.<sup>1</sup> Many melanomas that do not have BRAF mutations carry activating mutations in another oncogene, N-RAS. Signaling mediated by BRAF and N-RAS has proved to be a driving force in the growth of melanomas, and inves-

tigators are now developing therapies directed at this pathway. However, a complete understanding of the genetics of melanoma remains a distant goal.

In this issue of the *Journal*, Curtin et al. (pages 2135–2147) bring us closer to that goal (see diagram). They studied the DNA profiles of a diverse set of melanoma samples from acral and mucosal sites as well as the usual cutaneous melanomas. Cutaneous samples were also characterized according to the degree of solar elastosis, a marker of chronic sun-induced damage. In addition to determining the frequency of BRAF and N-RAS mutations, the authors also used a technique called array-based comparative genomic hybridization to scan the whole genome.

The genome of a cancer cell often diverges from that of the

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