Cervical Carcinoma and Human Papillomavirus:
On the Road to Preventing a Major Human Cancer

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Three papers in this issue of the Journal cover important aspects of high-risk human papillomavirus (HPV) infections: the infection as an indicator of high-risk lesions (1), strain variation as an indicator for a high risk of disease progression (2), and a phase I clinical trial revealing the potent immunogenicity of the three vaccine preparations tested (3).

The question of HPV identification as a screening tool in comparison to conventional cytology resulted in controversial discussions for quite some time. The article by Solomon et al. (1) reveals that the Hybrid Capture 2™ test for HPV detection has a higher sensitivity to detect cervical intraepithelial neoplasia grade 3 or worse and a specificity comparable to that of a single additional cytologic test, indicating atypical squamous cells of undetermined significance (ASCUS) or worse. Related findings, not specifically restricted to ASCUS, were also presented recently by another group (4). It is of interest to note that competing test systems are presently under development that take advantage of the ability of these viruses to induce selectively in the infected cells a high level of the cyclin-dependent kinase inhibitor p16INK4 as indirect evidence for high-risk HPV infection (5). Cells overexpressing this protein can be visualized readily by specific immune staining. It can be anticipated that test systems with higher specificity and sensitivity will become available to improve both the early diagnosis of HPV infections and, particularly, of progressing cervical lesions. The article by Solomon et al. (1) provides an excellent basis for future comparisons in randomized trials.

The HPV16 strain variation as a specific risk factor for cervical cancer had been postulated before by a number of groups. Hildesheim et al. (2) are to be commended for presenting convincing evidence for the role of strain variants in a prevalent case–control study within a 10,000-women, population-based cohort in Costa Rica. Multiple base substitutions within the long coding region (LCR) compared with the prototype HPV16 (6) were found at much higher rates than expected in high-grade lesions and cervical cancer biopsy specimens. The authors speculate on “a direct effect of the LCR variants detected here or to an indirect effect resulting from linkage disequilibrium with variations present in other regions of the viral genome.” An alternative and even more likely possibility is modification of the composition of cellular transcription factors binding and regulating the viral LCR. The tight regulation of high-risk HPV transcription by AP-1 homodimers and heterodimers has been shown before [reviewed in (7)]. The dimeric AP-1 binding factor is regulated in its composition by signaling cascades triggered by cytokines, particularly by tumor necrosis factor-α. In cervical carcinoma cells, this signaling cascade is inactive and is probably also interrupted by modifications in host-cell genes (8). The data provided by Soto et al. (8) implied previously the existence of a genetic predisposition for cervical cancer, if such modifications occur only in one allele in the germline and if they are compatible with cell survival. Indeed, such predisposition has recently been convincingly demonstrated by Magnusson et al. (9).

A number of industrial companies as well as research laboratories are engaged presently in preclinical and clinical trials of vaccines against high-risk HPV strains. Most approaches are based on the use of virus-like particles (VLP), representing only the structural proteins L1 or L1 and L2, for papillomaviruses initially established by Zhou et al. (10) and also used by the same group for early immunizations (11). The article by Harro et al. (3) represents the first published report after conclusion of a phase I safety and immunogenicity trial in adult volunteers of an HPV16 L1 VLP vaccine. This vaccine is highly immunogenic and well tolerated, even without adjuvant, as is also shown previously for an HPV6b VLP vaccine (12). The prospects for this vaccination are remarkably promising. On the basis of similar studies in dogs, rabbits, and cattle, effective prevention can also be expected from the human vaccine. If this turns out to be true and if the vaccine would be applied globally, prevention of infection by the most prevalent high-risk HPV types could theoretically prevent more than 300,000 cervical cancer cases per year worldwide.

The vaccination story has come a long way: The initial postulation of a role of HPV in cervical cancer (13), the demonstration of specific HPV types in cancer biopsy specimens and cervical carcinoma cell lines (6,14), and even the demonstration of specific integration and gene expression patterns in tumors and cell lines (15,16) were met with remarkable skepticism by several epidemiologists (17). They questioned the validity of previous work, and some had substantial difficulty reconciling the high incidence and persistence of HPV infections in the general population with a role in a human malignancy of a comparatively much lower incidence rate. In addition, other infectious agents, in particular, herpes simplex virus type 2, had been considered for a long time to be the prime candidates for the etiologic agents of this cancer [reviewed in (18)]. Even though the in vitro immortalizing properties of so-called high-risk HPV types for human cells had already been revealed as of 1987 (19–21) and the first (admittedly not state of the art) epidemiologic studies had been conducted clearly implying the role of HPV in cervical cancer (22), it was stated in a publication of the International Agency for Research on Cancer in 1989 that “the available data, although suggestive, do not allow further inferences on causality” (23). Well-controlled case–control stud-
ies were eventually performed by this group and published 3 years later. They were taken as firm evidence for HPV causality in cervical cancer (24,25).

In the personal experience of this author, up to this period it has not been possible to convince the pharmaceutical industry to consider the initiation of vaccination programs against high-risk HPV infections and, in all likelihood, several years have been lost. If we calculate an annual global incidence rate of 400,000 cases per year globally (26), this delay may turn out to be costly.

REFERENCES


