
CERVICAL CANCER EPIDEMIOLOGY AND RATIONALE FOR HUMAN PAPILOMAVIRUS (HPV) RELATED PREVENTIVE STRATEGIES

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On several occasions, estimates of the burden of HPV infections and of the closely associated cervical lesions have been produced. Data on invasive cervical cancer extrapolated to the existing population indicate for Europe some 65.000 new cases per year and an age-standard rate of 13 new cases per 100.000 per year. Data on genital HPV-DNA prevalence in representative samples of populations in different countries are limited. Typically the proportions of HPV-DNA carriers have been placed in the 15-40% range in the young, sexually active, age groups and between 3-10 % range in the 35 and above age groups. Prevalence in the male external genitals is only available for a few countries and the evidence suggests that may be roughly similar to the prevalence in women.

THE ASSOCIATION OF HPV AND CERVICAL CANCER

State-of-the art amplification techniques have unequivocally shown that in adequate specimens of cervical cancer HPV-DNA can be detected in 90 to 100% of the cases as compared to a prevalence of some 5-20% from cervical specimens of women identified as suitable epidemiological controls. Detailed investigations of the few cervical cancer specimens that appear as HPV DNA negatives in most series has been occasionally conducted and the results strongly suggest that these are largely false negatives. As a consequence, the claim has been made that this is the first *necessary cause* of a human cancer ever identified, providing a strong rationale for the use of HPV tests in screening programs and for the development of HPV vaccines.

RISK ESTIMATES FROM IARC'S CASE CONTROL STUDIES

The pool of IARC studies are large enough to provide, for the first time, type specific risk estimates for 18 types. The adjusted Odds Ratios for HPV DNA detection (the factor by which the reference risk of cervical cancer is multiplied if HPV DNA is detected) was OR any single type = 172.6 (95%CI: 122.2-243.7). Type specific risk estimates were as follows: HPV 16: OR= 435; HPV 18: 248; HPV 45 OR= 198; HPV 31 OR= 124; HPV 33 OR=374; HPV 35 OR=74; HPV51, OR= 67; HPV 52 OR= 200; HPV 58 OR= 115; HPV 59 OR= 419. The risk for any given high-risk type was not statistically different from the risk reported for HPV 16. The risk related to the presence of multiple HPV types in the specimen is no different from the risk linked to a single HPV type. The standard estimates of the attributable fraction AF %, (the proportion of disease that is related to HPV DNA) derived from these and most other studies range from 90 to 98%. The practical conclusions from these analyses

strongly indicates that, under current evidence, group testing of clinical specimens for a cocktail of high risk types should be sufficient for screening and patient management. One of such tests, Hybrid Capture 2 (HC2), is commercially available and progressively introduced in clinical practice. Individual typing remains necessary in research settings and for studies evaluating therapeutic or preventive type-specific HPV vaccines.

HPV TESTING IN SCREENING PROGRAMS

Cervical cytology has played an important role in screening and clinical management of cervical lesions. A recognized barrier is, however, the limited sensitivity and reproducibility of cervical cytology. It has been suggested that screening based on HPV-DNA testing may prove easier to implement and sustain, and considerable efforts are currently being devoted to the testing of this hypothesis.

Ideally HPV screening tests should detect all CIN 3 / HSIL and cervical cancer. Both HC 2 and GP5+/6+ PCR/EIA have sensitivities for CIN 3 and cervical cancer at least equal and in most studies significantly better than cervical cytology. Specificity of HPV tests is age dependent. In the young age groups the specificity of the HPV tests is lower than cytology and, in the age groups 35 and above (again country-dependent), the specificity of both tests is similar. Recent studies, in which HC 2 and GP 5+/6+ were used, showed that, in combination, women with both normal cytology and absence of HPV DNA have an extremely low risk of developing cervical cancer in the 10+ subsequent years. Major gains in effectiveness and cost reduction are to be expected from increasing screening intervals and reducing the total number of visits requested per lifetime in most cytology-based screening programs.

HPV TESTS IN THE TRIAGE OF MINIMAL CERVICAL ABNORMALITIES

One of the first applications of HPV testing in clinical practice was the secondary triage of women referred for colposcopy because of an abnormal Pap smear. In the U.S., the adoption of the Bethesda system (TBS) for cervical cytology reports dramatically increased the proportion of Pap smears with cytological abnormalities that merited clinical attention. It is now accepted that smears with equivocal or minor grade abnormalities represent some 4-7% of all Pap smears in the US, a considerable workload for the purposes of clinical decision-making.

The best evidence on the role of HPV testing as an alternative method to repeated cytology in the presence of an ambiguous abnormal cytology is being provided by the Kaiser Permanente study in 1999 and the ALTS trial in 2000. The Kaiser Permanente study used concomitant testing focused exclusively on ASCUS as the referral smear's presumptive diagnosis. The sensitivity to detect HSIL or cancer was 89% for HPV and 76% for Pap, with equivalent specificities for both tests (64%).

The ALTS trial is a National Cancer Institute (NCI) coordinated randomized clinical trial designed to determine the optimal management plan separately for LSIL and ASCUS cytologic abnormalities. The LSIL component of the ALTS trial had the HPV triage arm terminated prematurely because of the interim observation of a very high rate (83%) of oncogenic HPV positivity. Such high HPV prevalence in LSIL is rarely reproduced in other studies, reflecting the variability in the diagnosis of LSIL. The authors of the ALTS trial concluded that in the US setting, there would be limited value in using HPV testing in triaging LSIL cases for colposcopy.

In contrast, the ASCUS component of the trial reinforced the findings of the Kaiser Permanente study. HPV testing yielded 96% sensitivity to detect both CIN2+ and CIN3+ histologically-confirmed lesions while a repeat Pap at the lowest threshold of ASCUS produced a significantly lower sensitivity of 85% for both definitions of lesion severity. The sensitivity of a repeated cytology at a threshold level of CIN3+ was as low as 44%.

The proportions of women who would have to be referred for colposcopy due to positivity in these tests were 56% and 59%, respectively. The trial concluded that HPV testing was a viable option in the triage and management of ASCUS smears.

WHAT CAN WE ANTICIPATE FOR VACCINE COMPOSITION

Given the strong relationship between HPV infections and cervical cancer, prevention of persistent HPV infections seems to be a desirable target and perhaps the only realistic option for developing countries. Since HPV type-specific cross protection is limited, one of the central issues in exploring products destined to widespread use is the number of viral types that are to be included. The cumulative prevalence of HPV types in over 2000 cases of invasive cervical cancer from over 25 countries shows that four HPV types, 16, 18, 45 and 31 explain close to 80% of the types involved in cervical cancer worldwide. The variability is somehow less marked for cervical adenocarcinomas, where HPV types 16, 18, 45 and 59 account for 93% of the types found in cases.

Therapeutic vaccines may offer interesting alternatives in populations where a large fraction of young adult women are already permanent carriers of HPV DNA. These products incorporate modified fragments of the E6 and/or E7 genes, the viral products consistently expressed in persistent infections and in cervical cancer. Chimeric VLPs have been shown to induce antigen-specific protection in mice from challenge with E7-expressing tumor cells.

RECOMMENDED READING:

Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002; **55**:244-65.

Muñoz N, Bosch FX, de Sanjose S, et al. Epidemiological classification of Human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; **348**:518-27