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Cervical cancer screening: epidemiology as the necessary but not sufficient basis of public health practice

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Background

This special section of **Preventive Medicine** is devoted to cervical cancer screening. It covers why and how testing for human papillomavirus (HPV) is replacing cytology (the Papanicolaou or Pap test) as the primary cervical screening test in varied settings around the world. In short, HPV testing is coming and the role of cytology will be reduced; however, this collection of evidence summaries, guidelines, and editorials aims to illustrate the variety of ways the changeover will occur globally.

More broadly, this special section illustrates the importance and limits of epidemiology as the "basic science of public health". The conclusion of the section is that given an established epidemiologic set of scientific facts and validated prevention tools, real-life concerns that vary by region will determine which public health strategies are used. We should neither minimize nor exaggerate the importance of epidemiology in Public Health; its role varies as a medical research field matures from etiology to preventive methods development to implementation. Epidemiology played an important role in establishing via interdisciplinary studies that a dozen types of HPV cause virtually all cervical cancers and precursors worldwide. Epidemiologic methods were absolutely crucial in validating a now-excellent group of prophylactic HPV vaccines and sensitive screening tests. But in the U.S. at least, epidemiology has just one seat at a crowded table when discussing health care policy and the practical management of screen-positive women. Local policy concerns, varying views and tolerances of safety, patient and clinician advocacy, funding constraints, and many other non-scientific factors outweigh epidemiologic data in deciding which prevention programs are created and supported.

Cervical screening presents a nearly unique opportunity to examine the impact of resource levels on cancer prevention programs. Cervical cancer is a globally uniform disease in terms of etiology and pathogenesis. The same limited set of HPV types cause cervical cancer everywhere, and the natural history of cervical carcinogenesis is consistent throughout the world. Because HPV vaccination is still new, HPV prevalence and secondary prevention

efforts are the main determinants of the cervical cancer burden. Thus, we can examine varying regional public health responses without regional differences in cancer etiology and natural history.

Introduction to the articles

The special HPV section presents the evidence supporting a switch from cytology to HPV testing, then contrasts the regional responses. It consists of the following parts: First, it presents three complementary evidence reviews supporting HPV testing. To begin, Tota et al. [1] [In this issue] from Canada summarize the overwhelming evidence that testing for the dozen types of HPV that cause cervical cancer is more sensitive and reproducible than cytology. Because the high proportion of women with HPV infection and associated lesions would control or clear infections on their own, universal treatment of HPV-positive women should be avoided if possible to avoid overtreatment. Thus, there is the need for distinguishing those women at most risk of cancer from among the large group of HPV-positives (called “triage” of the positive women). Accordingly, the second review by Tota et al. summarizes possible triage methods designed to help clinicians decide which HPV-positive women need colposcopy/biopsy or even immediate treatment [2] [In this issue]. For those that doubt that HPV testing will replace cytology, the advent of prophylactic HPV vaccination settles the case; Rossi et al. summarize the new Italian guidelines that outline how screening programs must adapt as vaccinated age cohorts reach the age of screening [3] [In this issue]. The predictive value of a positive cytologic test decreases in vaccinated cohorts, making HPV testing with assays that provide partial HPV genotyping the logical screening method.

The three-part presentation of evidence and guidelines is followed by a series of five commentaries. All accept the evidence presented by the reviews; however, the authors demonstrate in their differing conclusions how varying resource levels will shape adaptation of cervical screening programs. Kinney and Huh [4] [In this issue] discuss their view of cervical screening policies in the US, where safety is paramount and program efficiency is less important. Wentzensen and Arbyn [5] [In this issue] show that other high-resource countries are tending to balance safety and efficiency. Rodriguez and Salmeron [6] [In this issue] describe how high middle-income countries are striving for the best possible program impact and wide coverage with available resources. Gage and Maza [7] [In this issue] present the situation in low middle-income countries where screening remains feasible but resource limitations are pronounced. Finally, Kuhn and Denny [8] [In this issue] argue for a switch to HPV testing even in low-resource regions.

A personal summary view of cervical screening in evolution

In my opinion, the main facts of HPV etiologic epidemiology and cervical carcinogenesis are beyond questioning. And I believe that, among experts, there is an emerging consensus that HPV testing is theoretically the optimal available primary screening test, but that its optimal implementation is far from settled.

Alternative screening methods continue to be used and promoted, but have waning support. In my view, low-cost visual screening (VIA, or visual inspection with acetic acid) is not accurate or reproducible as performed, for the identification of precancerous lesions, and should be replaced when possible. It is more effective in identification of cancer, permitting life-saving downstaging when excellent treatment facilities are nearby. But this is a rare situation. It is conceivable that current efforts to develop image recognition apps that could be used with smartphone cameras might improve the reproducibility and even accuracy of VIA, but otherwise VIA is a transitional screening method.

Cervical cytology, which must be frequently repeated to achieve sufficient sensitivity, has failed to extend beyond high-resource environments despite many decades of public health effort. The reasons are beyond the scope of this short comment, but the facts “speak for themselves”. HPV testing is more sensitive but less specific than cytology, mandating extension of screening intervals when HPV testing is negative. It can be made simpler and more reproducible than cytology. But triage is important because treatment of all infected women is excessive; the great majority of infections with the “carcinogenic” HPV types are controlled or otherwise clear without causing cancer.

At present, the most commonly recommended triage options among women screening HPV positive, when resources are available, are partial HPV typing combined with cytology or cytology-like methods. The classification by IARC of a dozen HPV types as carcinogenic explicitly did NOT consider carcinogenic strength and were NOT meant to dictate inclusion of all carcinogenic types in the creation or use of HPV assays [9]. The carcinogenic HPV types vary profoundly in risk of cancer, mandating different management of the highest risk (especially HPV16) versus lowest risk types. To promote HPV testing in lower-resource regions, it is perfectly reasonable to consider restriction of HPV testing to match the capacity of treatment staff and facilities.

Other triage options are not as advanced. Molecular tests to triage HPV-positive results are in early development (e.g., methylation assays) and visual triage methods are again not very accurate. It is difficult visually to distinguish HPV infections from precancer, particularly in the presence of inflammation that is common in many settings. Computer-assisted image recognition apps are in development, and might prove useful but, for now, the choice of triage method remains unsettled.

It turns out that detailed implementation of HPV primary screening to replace cytology reveals many choices reliant on value judgments and not risk assessment, particularly when resources are limited. Controversial areas included acceptable costs and effort, choices of safety and action thresholds, and the role of the clinician in the integration of test data vs. apps and guidelines.

As the commentaries by experts show, cervical cancer prevention is viewed very differently in different settings. Regardless of what prevention strategy is chosen, it should be scientifically and medically defensible. On the extremes, I would personally argue that continued dependence on VIA, or excessively frequent repetition of cytology and HPV cotesting, are not justified by the data. As different strategies are applied worldwide, the

hope is that they will be translatable and represent different societal conclusions sharing a jointly understood scientific base.

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Highlights

- Primary cervical screening with HPV testing is more sensitive than cytology.
- HPV vaccination further supports HPV screening with partial genotyping.
- Positive HPV testing requires secondary “triage” to minimize overtreatment.
- Societal risk tolerance and resource level influence the switch to HPV testing.
- Generally, epidemiologic consensus is just one influence on public health response.