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Chapter 29: Knowledge gaps and priorities for research on prevention of HPV infection and cervical cancer

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Abstract

The recognition that human papillomavirus (HPV) infection is the necessary cause of cervical cancer brought new prevention paradigms in screening and HPV immunization. We now face many questions about how to implement an ambitious evidence-based agenda for cervical cancer prevention. Much is known about the epidemiology and natural history of HPV infection but several key variables remain to be elucidated. Research on HPV transmission requires new study designs to provide useful insights into preventive strategies. HPV testing has carved a niche in clinical practice but to consolidate its role in screening still requires evidence of long-term benefit. The rapidly evolving field of HPV diagnostics has contributed useful information concerning the value of HPV typing. Other screening methods hold promise in specific settings. The decade-long process that brought HPV vaccines to the doorstep of public health application is over. Many questions remain concerning long-term efficacy, correlates of protection, age of vaccination, and delivery. As vaccination makes inroads as a cancer control strategy, screening practices must be reformulated to maximize the synergy between primary and secondary prevention. Research on how to achieve an efficient combination of these modalities is yet to begin, but mathematical models have provided a useful road map for field-testing of promising algorithms. Daunting questions loom large concerning delivery of vaccines to those populations that need it the most. The field of HPV and cervical cancer prevention has never been so multi-disciplinary. A new era has begun and the challenges are many.

Keywords: Cervical cancer; Human papillomavirus; Vaccine; Screening; Cytology; Prevention; Health economics; Models

1. Preamble

In the past 20 years basic, clinical, and population health research on the prevention of cervical cancer have progressed rapidly. The recognition that H infection was the central necessary cause of cervical cancer created new fronts for prevention via improved screening methods and immunization against HPV via vaccination. Owing to this successful track record the research community now faces a long list of needs and priorities from policymakers to assist them in implementing an ambitious evidence-based agenda for cervical cancer prevention. This chapter provides a summary of gaps in knowledge and needed research directions on HPV

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and cervical cancer. It was written by this monograph's section editors as a consensus document that collected views expressed by international experts in all areas of cervical cancer control and prevention. The headings below reflect key methodological and content areas covered in the monograph. The few references are given to inform readers about main sources of reading material that contain pointers to other primary documents. The individual monograph chapters contain an extensive, yet selected, bibliography concerning the individual topics of relevance in cervical cancer control.

2. HPV as a major public health problem

This section included chapters that provided an overview of knowledge concerning the burden of illness associated with HPV infection with a focus on cervical and other anogenital cancers. Although much is known about the role of HPV infection as the primary driver of the natural history of cervical neoplasia, there are significant gaps in our understanding (Table 1).

2.1. What is established

In spite of the existing efforts to register and monitor trends in the incidence of cervical cancer, extensive areas of the world still suffer from considerable uncertainty in this respect. These include large populations in Asia and Africa as well as some populations in Eastern Europe and Latin America. Case–control studies and independent cohort investigations have conclusively established that infection by high-risk HPV types is the necessary causal precursor in cervical carcinogenesis (reviewed in [1,2]). These studies have unveiled a wealth of information concerning the ancillary role of cofactors and on the epidemiology of HPV infection. Table 1 summarizes the main research achievements that are of relevance in prevention and gaps in our knowledge. The main thrust of research in epidemiology has been the demonstration of the causal role of HPV infection in cervical cancer. Natural history research has dealt with assessment of viral exposure as an intermediate endpoint on the basis of constantly evolving HPV DNA tests that have reached a very

Table 1
Essential findings, gaps in knowledge, and priorities for research on the epidemiology of HPV infection and cervical cancer

Research areas	Findings that are essential to assist prevention efforts	Gaps in knowledge and research priorities
Burden of cervical cancer	Methods to estimate the number of new cases per world region; secular trends for countries with well-developed cancer registries	Estimates from extensively populated areas in the world (i.e., China and India); HPV-type distributions in individual regions/countries in cervical cancer; relative contributions of HPV-16/18 per region/country
Role of HPV in cervical cancer	HPV genotypes associated with risk; persistent infection as the key causal intermediate; knowledge that most important HPV types are relatively constant in etiologic fraction throughout the world	Risk factors for progression to invasion; role of cofactors acting "downstream" from HPV infection; duration of lesion sojourn time; role of cofactors upstream from HPV infection
Role of HPV in other anogenital cancers	Lower but substantial etiologic fraction for cancers of the vulva, vagina, anus, and penis	Concerted multi-centre studies to pool cases and controls to obtain more accurate estimates of risks for these rarer tumors attributed to different HPV types and the role of cofactors
Epidemiology of genital HPV infection	Sexual activity is the key behavioural risk factor with strong mediating role of age; HPV type distribution among lesion-free women reasonably well established across continents	Identify immunological factors and other determinants of regression, persistence and progression; geographical differences among the minor oncogenic HPV to inform composition of next generation vaccines; differences among HPV types in risk factors and oncogenic potential; distribution of HPV types in atypical squamous cells of undetermined significance (ASCUS) smears to help inform next generation of HPV typing tests for triage; geographical information on the burden of genital warts and HPV type attribution
Natural history of HPV infection	Duration of HPV infection is 8–16 months on average, high-risk (HR)-HPVs more persistent than low-risk (LR)-HPVs; HPV-16 more persistent in some populations; most infections clear within 1 year	Does HPV infection segregate to the basal layer of the epithelium and becomes undetectable (concept of latent infection); What is the genesis of infections later in life? Can new acquisition be differentiated from reactivation later in life? Standardization of research on HPV persistence (frequency and mode of sampling and testing); role of antibody and cell-mediated immunity
Transmission of HPV infection	Sexual transmissibility likely to be among the highest among all STIs	Studies in forming couples to determine infectivity, risk factor for transmission; relation between infectivity and viral load; role of sexual networks; importance of non-sexual routes in transmission; differences between HR- and LR-HPVs; inconsistent findings regarding condom protection