Introduction: Future Research Directions in the Epidemiology of Human Papillomavirus and Cancer

F. Xavier Bosch, Mark Schiffman, Diane Solomon

The causal link between human papillomavirus (HPV) and cervical cancer is now established beyond doubt and the association has become an important model of viral carcinogenesis. The corollary in practical terms is that cervical cancer does not occur without the persistent presence of HPV-DNA. Research on HPV-negative cervical cancers is no longer a priority, because such cases are exceedingly rare (i.e., the non-epithelial cervical cancer types) and usually the result of measurement error of some kind.

The implications for cancer prevention are revolutionary. Screening with HPV tests that cover approximately 15 oncogenic or "high-risk" HPV types can effectively target all women with prevalent or incipient cervical cancer worldwide. Likewise, polyvalent prophylactic HPV vaccines should be able to prevent a predictable fraction of the cases of cervical cancer in a given population.

In reaction to new etiologic evidence and improved technology, cervical cancer epidemiologic and preventive efforts are being reshaped throughout the world, based on the resource levels of the different regions. This monograph was designed to consider what studies on HPV and cancer are most likely to be useful in the decade ahead.

With regard to etiology, future molecular epidemiologic research will concentrate on the cofactors for HPV carcinogenesis as well as on the steps and mechanisms by which an extremely common and largely trivial infection may occasionally induce cancer in the absence of early detection and treatment of intraepithelial precursors. Issues of considerable interest include the role of known and suspected environmental cofactors, the determinants of the immune response to the viral infection, the interaction between the host and the virus, and the relevance of different HPV types and variants.

With regard to prevention research, in developed countries, epidemiologists are currently helping to evaluate opportunities to reinforce screening programs by adding HPV testing to cytology. Scientific evidence supporting the value of HPV testing as an additional screening option is now abundant and consistent. Cytology itself is improving, creating additional options. Medical societies dealing with cervical cancer prevention are benefiting from the results of rigorously conducted controlled studies at the time they are updating their screening protocols. An opportunity lies ahead to rationalize the clinical management of such women in the context of a truly intelligent and cost-effective preventive medicine policy. It would be desirable to avoid overuse of technology among affluent groups particularly in the United States where screening sensitivity is valued so much more highly than specificity. Guidelines will be needed to optimize the care of women with novel diagnoses such as "persistent HPV DNA detection without abnormalities at colposcopy or cytology," "minor cytological abnormalities that are repeatedly HPV negative," and so on.

Although new technology is most likely to be introduced first into developed countries, low-resource regions experience most of the burden of cervical cancer. Epidemiologists will be involved in supporting efforts to make preventive methods available to extensive areas of the developing world. Some of the new technology, if it is made into high-throughput equipment, may be transferable to countries with a medium level of industrial development and current lack of any meaningful screening program. Specifically, if fast and inexpensive HPV tests can be developed, it is likely that in the years to come, some form of HPV testing will be adopted for primary screening in moderate resource regions that currently do not have firmly established cytology programs. Validation of these emerging testing systems under field conditions will likely be a major task.

Other innovative strategies and technologies could fill this niche instead and some are in advanced stages of development and testing. Epidemiologists will be evaluating direct visual methods, the use of electro-optical probes, and new molecular markers. Whichever test can be made reliable and affordable will have an enormous market and a profound impact on cancer burden.

The evaluation and introduction of HPV vaccines is a promising area for cervical cancer prevention for a large number of populations. Recent results obtained with an HPV 16 vaccine have further raised already-high expectations. Immune prophylaxis has been the cornerstone of preventive medicine and the only strategy known to have eradicated or radically reduced some major viral diseases from the human population.

However, human research on HPV vaccination is only beginning and will certainly require product development and the conduct of trials for a number of years. Once a vaccine is proven to be safe and effective, issues of accessibility to women in all countries will become of prime importance. Vaccines amenable to mass production and wide distribution will need to be inexpensive, temperature resistant, and dependent on a limited number of boosters. They should have a therapeutic component and cover a wide spectrum of viral types. When these vaccines are available, epidemiologists are likely to focus on the conduct of comparative trials and to monitor the vaccination impact on cervical cancer incidence and mortality. In terms of saving lives, the predominance of cervical cancer in countries with low resources should again be our collective focus.

Investigation of the role of HPV in nongenital cancer sites is another promising field, with cancers of the upper aero-digestive

Affiliations of authors: F. X. Bosch, Epidemiology and Cancer Registration Unit, Catalan Institute of Oncology, Avda. Gran Via, s/n Km 2,7,08907 L'Hospitalet de Llobregat, Barcelona, Spain; M. Schiffman, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD; D. Solomon, Breast and Gynecologic Cancer Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD.

Correspondence to: F. Xavier Bosch, M.D., Epidemiology and Cancer Registration Unit, Catalan Institute of Oncology, Avda. Gran Via, s/n Km 2,7,08907 L'Hospitalet de Llobregat, Barcelona, Spain (e-mail: x.bosch@ico.scs.es).

Journal of the National Cancer Institute Monographs, No. 31,

tract and skin cancer as some of the major candidates. As HPV studies are extended beyond anogenital neoplasia, further developments in HPV serology are expected to be crucial to foster additional epidemiological research on HPV infections and human cancer.

This monograph is a cooperative effort of a sizable group of senior epidemiologists and interdisciplinary colleagues, who met in June 2002 at the National Cancer Institute, Bethesda, Maryland, to discuss the ideas contained within the chapters. In the review and editing process there was no requirement for consensus on all points and therefore the chapters should be viewed as a series of forward-thinking expert commentaries, rather than a review of evidence or a policy document. Efforts have been made to consider topics from an international perspective. However, it is recognized that the preventive conclusions suggested in some of the chapters cannot be generalized to extensive areas of the world that are currently underserved.

It has been a pleasure for the editors to coordinate this project and we hope the readers will find interesting suggestions for their future work. We acknowledge in particular the experts who attended as reviewer–discussants, and contributed greatly to this monograph, without benefit of authorship. They include Robert Burk, Jack Cuzick, Joakim Dillner, Silvia Franceschi, Barbara Moscicki, Julian Peto, and Peter Snijders.