

Prevention of Genital HPV Infection and Sequelae: Report of an External Consultants' Meeting

Division of STD Prevention

December 1999

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for HIV, STD, and TB Prevention
Division of STD Prevention
Atlanta, Georgia 30333

Copyright Information

All material contained in this report is in the public domain and may be used and reprinted without special permission; citation to source, however, is appreciated.

Suggested Citation

Division of STD Prevention. Prevention of Genital HPV Infection and Sequelae: Report of an External Consultants' Meeting. Department of Health and Human Services, Atlanta: Centers for Disease Control and Prevention (CDC), December 1999.

Copies can be obtained from the Office of Communications, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, Mailstop E-06, Atlanta, Georgia 30333.

This report is available by Internet via the CDC home page at:
http://www.cdc.gov/nchstp/dstd/Reports_Publications/99HPVReport.htm

Acknowledgments

This report was prepared by the following staff in the Division of STD Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention: John M. Douglas (currently affiliated with the Denver Department of Public Health, Denver, Colorado), Katherine M. Stone, and Michael E. St. Louis; Elizabeth R. Unger in the Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention; and Robert Smith of the American Cancer Society.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the Department of Health and Human Services.

Table of Contents

Abbreviations Used in This Report	vii
External Consultants	viii
Executive Summary	1
Introduction	5
Overview	6
Recommendations From The Workgroups	9
1. Role of HPV testing in cervical cancer screening	9
Background	9
Workgroup Discussion	10
Recommendations for public health/prevention activities	11
Research/evaluation priorities	11
2. Cervical cancer screening in adolescents	12
Background	12
Workgroup discussion	12
Recommendations for public health/prevention activities	13
Research/evaluation priorities	13
3. Non-vaccine modalities for primary prevention of genital HPV infection	13
Background	13
Workgroup discussion	14
Recommendations for public health/prevention activities	15
Research/evaluation priorities	16
4. Preparedness for prophylactic HPV vaccines	16
Background	16
Workgroup discussion	17
Research/evaluation priorities	18
5. Provider, patient, and public awareness	19
Background	19
Workgroup discussion	19
Provider awareness	20
Recommendations for public health/prevention activities	20
Research/evaluation priorities	20
Patient awareness	20
Recommendations for public health/prevention activities	20
Research/evaluation priorities	20
Public awareness	20
Research/evaluation priorities	20
6. Anal Cancer	21
Background	21
Workgroup discussion	21
Research/evaluation priorities	22

7. Surveillance for genital HPV infection and sequelae	22
Background	22
Workgroup discussion	23
Recommendations for public health/prevention activities	23
Research/evaluation priorities	24
References	25

Abbreviations Used in This Document

ACS	American Cancer Society
AGUS	Atypical glandular cells of undetermined significance
AIDS	Acquired immunodeficiency syndrome
ALTS	ASCUS-LSIL Triage Study
ASCUS	Atypical squamous cells of undetermined significance
ASIL	Anal squamous intraepithelial lesion
CDC	Centers for Disease Control and Prevention
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CPT	Certified Procedural Terminology
CSTE	Council of State and Territorial Epidemiologists
DCPC	Division of Cancer Prevention and Control
DNA	Deoxyribonucleic acid
DSTD	Division of Sexually Transmitted Diseases Prevention
DVRD	Division of Viral and Rickettsial Diseases
FDA	Food and Drug Administration
GW	Genital warts
HC-II	Hybrid Capture II
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
ICD	International Classification of Disease
JORP	Juvenile onset respiratory papillomatosis
LEEP	Loop electrical excision procedure
LSIL	Low-grade squamous intraepithelial lesion
mRNA	Messenger ribonucleic acid
MSM	Men who have sex with men
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCHSTP	National Center for HIV, STD, and TB Prevention
NCID	National Center for Infectious Diseases
NDTI	National Disease and Therapeutic Index
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NPCR	National Program of Cancer Registries
PCR	Polymerase chain reaction
PID	Pelvic inflammatory disease
PV	Papillomavirus
RCT	Randomized clinical trial
RRP	Recurrent respiratory papillomatosis
SDS	Sodium dodecyl sulfate
SEER	Surveillance Epidemiology and End Results
SIL	Squamous intraepithelial lesion
STD	Sexually transmitted disease
VLP	Virus-like particle

External Consultants

Adaora A. Adimora, M.D., M.P.H., University of North Carolina School of Medicine, Chapel Hill, NC; **Linda L. Alexander, Ph.D., FAAN**, The American Social Health Association, Research Triangle Park, NC; **Thomas M. Becker, M.D., Ph.D.**, Oregon Health Sciences University, Portland, OR; **Karl Beutner, M.D., Ph.D.**, University of California, San Francisco, Vallejo, CA; **Gail Bolan**, California Department of Health Services, Berkeley, CA; **Virginia Caine, M.D.**, Marion County Health Department and Indiana University School of Medicine, Indianapolis, IN; **Willard Cates, Jr., M.D., M.P.H.**; Family Health International, Durham, NC; **Charles W. Ebel**, Independent Consultant, Durham, NC; **Maria Eugenia Fernandez-Esquer, Ph.D.**, UT-Houston School of Public Health, Houston, TX; **Dennis Fortenberry, M.D., M.S.**, Indiana University School of Medicine, Indianapolis, IN; **Sue J. Goldie, M.D., M.P.H.**, Harvard School of Public Health, Boston, MA; **H. Hunter Handsfield, M.D.**, University of Washington and Seattle-King County Department of Health, Seattle, WA; **Diane M. Harper, M.D., M.S., M.P.H.**, Dartmouth Medical School, Hanover, NH; **Penelope J. Hitchcock, D.V.M.**; National Institute of Allergy and Infectious Diseases, Bethesda, MD; **King K. Holmes, M.D., Ph.D.**, University of Washington, Seattle, WA; **Edward W. Hook, III, M.D.**, University of Alabama, Birmingham, AL; **David Jenkins, M.D.**, Nottingham University, Nottingham, UK; **Laura A. Koutsky**, University of Washington, Seattle, WA; **Robert J. Kurman, M.D.**, Johns Hopkins University School of Medicine, Baltimore, MD; **Attila T. Lorincz, Ph.D.**, Digene Corporation, Silver Spring, MD; **M. Michele Manos, Ph.D., M.P.H.**; Kaiser Permanente Division of Research, Oakland, CA; **Heather G. Miller, Ph.D.**, Research Triangle Institute, Washington, DC; **Anna-Barbara Moscicki, M.D.**, University of California at San Francisco, San Francisco, CA; **Evan R. Myers, M.D., M.P.H.**, Duke University Medical Center, Durham, NC; **Jorma Paavonen, M.D.**, University of Helsinki, Helsinki, Finland; **Joel Palefsky, M.D.**, University of California at San Francisco, San Francisco, CA; **Gary A. Richwald, M.D., M.P.H.**, National Coalition of STD Directors and Institute for Healthcare Advancement, Whittier, CA; **Michael W. Ross, Ph.D., M.P.H.**, WHO Center for Health Promotion Research and Development and University of Texas, Houston, TX; **Debbie Saslow, Ph.D.**, American Cancer Society, Atlanta, GA; **John Schiller, Ph.D.**, National Cancer Institute, NIH, Bethesda, MD; **Jane R. Schwebke, M.D.**, University of Alabama, Birmingham, AL; **Keerti V. Shah, M.D., Dr.P.H.**, Johns Hopkins School of Public Health, Baltimore, MD; **Robert Smith, Ph.D.**, American Cancer Society, Atlanta, GA; **Diane Solomon, M.D.**, National Cancer Institute, Rockville, MD; **Mark L. Welton, M.D.**, University of California at San Francisco, San Francisco, CA; **Cosette M. Wheeler, Ph.D.**, University of New Mexico School of Medicine, Albuquerque, NM; **Jonathan M. Zenilman, M.D.**, Johns Hopkins University School of Medicine, Baltimore, MD; **Gregory D. Zimet, Ph.D.**, Indiana University School of Medicine, Indianapolis, IN.

CDC Participants

Sevgi O. Aral, Ph.D., Division of STD Prevention (NCHSTP); **Harrell Chesson, Ph.D.**, Division of STD Prevention (NCHSTP); **Susan DeLisle, A.R.N.P., M.P.H.**, Division of STD Prevention (NCHSTP); **John M. Douglas, M.D.**, Division of STD Prevention (NCHSTP) and Denver Department of Public Health, Denver, CO; **Elamin H. Elbasha, Ph.D.**, Office of the Director (NCID); **Ted V. Ellerbrock, M.D., FACOG, Division of HIV/AIDS Prevention (NCHSTP)**; **Lauri Flatt**, Office of Communications (NCHSTP); **Rima F. Khabbaz, M.D., Division of Viral and Rickettsial Diseases (NCID)**; **Nancy C. Lee, M.D.**, Division of Cancer Prevention and Control (NCCDPHP); **William C. Levine, M.D.**, Division of STD Prevention (NCHSTP); **Harold S. Margolis, M.D.**, Division of Viral and Rickettsial Diseases (NCID); **Lauri Markowitz, M.D.**, Division of STD Prevention (NCHSTP); **Matthew T. McKenna, M.D., M.P.H.**; Division of Cancer Prevention and Control (NCCDPHP); **William C. Reeves, M.D.**, Division of Viral and Rickettsial Diseases (NCID); **Russell H. Roegner, Ph.D.**, Division of STD Prevention (NCHSTP); **Janet St. Lawrence, Ph.D.**, Division of STD Prevention (NCHSTP); **Michael E. St. Louis, M.D.**, Division of STD Prevention (NCHSTP); **Katherine M. Stone, M.D.**, Division of STD Prevention (NCHSTP); **Guoyu Tao, Ph.D.**, Division of STD Prevention (NCHSTP); **Elizabeth R. Unger, Ph.D., M.D.**, Division of Viral and Rickettsial Diseases (NCID); **Suzanne D. Vernon, Ph.D.**, Division of Viral and Rickettsial Diseases (NCID); **Judith N. Wasserheit, M.D., M.P.H.**; Division of STD Prevention (NCHSTP).

Executive Summary

Genital human papillomavirus (HPV) infection is the most common sexually transmitted disease (STD) in the United States and is of increasing public health concern, yet no prevention programs have been established. Certain HPV types cause abnormal Pap smears and are etiologically related to cervical, vulvar, anal, and penile cancers; other types cause genital warts, recurrent respiratory papillomatosis, and low-grade Pap smear abnormalities. Recommendations for programmatic activities, prevention research, and evaluation were developed by a group of invited experts who met in Atlanta on April 13-14, 1999. This consultation on “Prevention of Genital HPV Infection and Sequelae” was cosponsored by CDC’s Division of STD Prevention (DSTD), National Center for HIV, STD, and TB Prevention (NCHSTP); Division of Cancer Prevention and Control (DCPC), National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP); Division of Viral and Rickettsial Diseases (DVRD), National Center for Infectious Diseases (NCID); and the American Cancer Society (ACS). Discussions were focused around key questions for seven topics pertinent to prevention of genital HPV infection and sequelae: the role of HPV testing in cervical cancer screening, cancer screening in adolescents, non-vaccine approaches to primary prevention of HPV infection, preparedness for prophylactic HPV vaccines, public and provider awareness, prevention of anal cancer, and surveillance for HPV and cancer. Following a summary of the discussion of the issues in each core topic area, recommendations are listed. These include recommendations (summarized below) for programmatic public health/prevention activities ready for implementation in the near future as well as recommendations for prevention research or other evaluation activities. While these recommendations were made primarily as suggestions for CDC and ACS, many are also relevant for other organizations interested in prevention of genital HPV or related sequelae (e.g., the National Institutes of Health). The intent of this report is to stimulate long-term collaborative efforts among a variety of organizations.

Summary of Recommendations for Public Health/Prevention Activities for Genital HPV Infections and Sequelae

1. Role of HPV testing in cervical cancer screening

- a. CDC and ACS should acknowledge usefulness of HPV testing as an option in triage of women with ASCUS Pap smears.
- b. CDC or ACS should facilitate a meeting to review cervical cancer prevention modeling and assess cost-effectiveness of different strategies.

2. Cervical cancer screening in adolescents

- a. Because the large majority of cervical lesions in adolescents are self-limited, in those with low-grade cytologic abnormalities (e.g., ASCUS, LSIL) consideration should be given to conservative follow-up by repeat Pap smear rather than triage by HPV testing or early colposcopy/biopsy.
- b. CDC and ACS should recommend that the cytology should be collected first when Pap smear screening is conducted concurrently with STD testing.

3. Non-vaccine modalities for primary prevention of genital HPV infection

- a. Given the uncertainties about prevention of transmission of genital HPV to sexual partners, a standard script for providers to use in education /counseling should be developed and used.

4. Preparedness for prophylactic HPV vaccines - none ready for implementation.

5. Provider, patient, and public awareness

- a. CDC, ACS, and other professional organizations should draft and disseminate a consensus statement for use in professional educational materials of what has been scientifically established about genital HPV (as well as what is not known).
- b. In conjunction with provider materials, patient educational materials should be developed and distributed.

6. Anal Cancer - none ready for implementation.

7. Surveillance for genital HPV infection and sequelae

- a. Routine disease reporting of all genital HPV infections or for any specific types is not recommended at this time.
- b. CDC should conduct further analysis of the experience with genital warts reporting in various states to guide future directions in genital warts surveillance.
- c. Because routine reporting of CIS could be a useful adjunct to cancer surveillance, especially as HPV vaccine programs are implemented, problems encountered by SEER in the past should be examined and alternative approaches considered.
- d. Surveillance for HPV-related cancers should be enhanced in ways that contribute to understanding the causative role of HPV infection and prevention strategies (e.g., special studies using population-based cancer registries to ascertain sexual preference for men with anogenital cancers).

Summary of Research/Evaluation Priorities for Prevention of Genital HPV Infections and Sequelae

1. Role of HPV testing in cervical cancer screening

- a. demonstration projects to evaluate feasibility/cost-effectiveness of HPV testing for triage (high priority)
- b. HPV testing for triage in targeted high-risk populations (high priority)
- c. HPV testing in primary screening in developed countries (high priority)

- d. HPV testing in primary screening in developing countries (high priority)
- e. HPV testing in follow-up of untreated CIN 1 and treated CIN 2/3 (intermediate priority)

2. Cervical cancer screening in adolescents

- a. natural history of CIN 2 (prospective) and CIN 3 (comparative laboratory studies) in adolescents (high priority)
- b. long-term reproductive complications of ablative therapy in adolescents (high priority)
- c. long-term behavioral complications of ablative therapy in adolescents (intermediate priority)
- d. feasibility of recommending initiating Pap smear screening based on coitarche (intermediate priority).
- e. relative importance of rapidly progressive cancer in younger women (low priority)

3. Non-vaccine modalities for primary prevention of genital HPV infection

- a. assessment of HPV endpoints in ongoing condom and microbicide studies of STD/HIV prevention (high priority)
- b. efficacy of promotion of behavior change (reduction of partner number, etc.) to prevent HPV (high priority)
- c. definition of laboratory markers of genital HPV infectiousness (intermediate priority)
- d. benefit of treatment in preventing HPV transmission (intermediate priority)
- e. assessment of risk factors for persistent HPV infection and its role in transmission (intermediate priority)

4. Preparedness for prophylactic HPV vaccines

- a. assessment of rates and risk factors for HPV incidence, prevalence, and persistence in men (high priority)
- b. development of better sampling/ testing methods for incident HPV infection, including self-sampling (high priority)
- c. marketing research among the general public and providers about HPV vaccine acceptability (high priority)
- d. modeling studies of HPV transmission to target immunization programs (high priority)
- e. cost-effectiveness studies of HPV vaccines, including types 6/11 (high priority)
- f. studies of more convenient routes of delivery and dosing schedules of HPV vaccines (high priority)

- g. following efficacy trials, immunogenicity studies in other groups (men, young teens, STD clinics) (high priority)
- h. following licensure, studies of behavioral impact of vaccine use (high priority)

5. Provider, patient, and public awareness

- a. surveys of provider knowledge, attitude, and practices (intermediate priority)
- b. assessment of counseling/education needs of patients/partners and alternative methods (high priority)
- c. determination of psychosocial impact of diagnoses of HPV and of disclosure to partners (intermediate priority)
- d. surveys of knowledge and attitudes of the general public (intermediate priority)
- e. pilot public education programs to assess optimal form and content and drawbacks of messages (high priority)

6. Anal cancer prevention

- a. multicenter study of natural history and effectiveness/complications of therapy of anal LSIL and HSIL (high priority)
- b. anal Pap smear reproducibility, interobserver variability, optimal sampling technique, predictive value (high priority)
- c. assessment of role of HPV testing in anal cancer screening and triage of abnormal Pap smears (intermediate priority)
- d. assessment of risk factors for anal cancer in women and heterosexual men (intermediate priority)

7. Surveillance for genital HPV infection and sequelae

- a. population-based serosurveys enhanced by collection of mucosal swabs for DNA detection (high priority)
- b. sentinel approach for surveillance of HPV-related disease (high priority)
- c. enhance surveillance for JORP to better understand risk factors for transmission (high priority)
- d. expand/redefine ICD and CPT codes to capture better data on HPV-related procedures (intermediate priority)
- e. collaborate with organizations with electronic clinic databases to monitor genital warts trends (intermediate priority)

Introduction

Genital human papillomavirus (HPV) infections are sexually transmitted infections of increasing public health importance. Known for years as the cause of genital warts, there is a growing body of evidence demonstrating the etiological association with a variety of anogenital cancers. Furthermore, genital HPV infections are widespread among adults who have been sexually active and are estimated to have the highest incidence of any sexually transmitted disease (STD) in the U.S.¹. Although cervical cancer screening programs have been implemented in the U.S. and other developed countries for decades, public health agencies have not established programs for primary prevention of genital HPV infection nor attempted to modify existing cancer prevention programs to take advantage of the associated role of HPV².

With the steady progress being made against bacterial STD and the increasing recognition of the widespread prevalence of viral STD such as genital herpes and genital HPV infection, the Centers for Disease Control and Prevention (CDC) has initiated a Viral STD Prevention Initiative to systematically evaluate possible control strategies and a prevention research agenda for these infections. As part of this process, CDC's Divisions of STD Prevention (DSTD), Cancer Prevention and Control (DCPC), and Viral and Rickettsial Diseases (DVRD) and the American Cancer Society (ACS) co-sponsored an expert consultants' meeting on April 13-14, 1999 on "Prevention of Genital HPV Infection and Sequelae". Invited participants included 36 external consultants and 24 participants from CDC or ACS with expertise in the biology and epidemiology of HPV, clinical management, laboratory sciences, behavioral sciences, health education, health services research, and STD and cancer prevention program implementation and development. The meeting was organized around three workgroups during which participants discussed key questions in seven selected core topic areas pertinent to prevention of genital HPV infection and sequelae: the role of HPV testing in cervical cancer screening, cancer screening in adolescents, non-vaccine approaches to primary prevention of HPV infection, preparedness for prophylactic HPV vaccines, public and provider awareness, prevention of anal cancer, and surveillance for HPV and cancer. It should be noted that other important topic areas were not considered for specific workgroup discussion (e.g., increasing coverage of Pap smear screening in the population, treatment of HPV-related disease) because of lack of time and the perception that they would be more effectively addressed in other settings.

This report is organized around the seven core topic areas and represents the collective deliberations and recommendations from the workgroups and a concluding discussion session including all participants. Following a summary of the discussion of the issues in each core topic area, recommendations are listed. These include recommendations for programmatic public health/prevention activities ready for implementation in the near future as well as recommendations for prevention research or other evaluation activities. While these recommendations were made primarily as suggestions for CDC and ACS, many are also relevant for other organizations interested in prevention of genital HPV or related sequelae (e.g., the National Institutes of Health). The future response to these recommendations will optimally be collaborative among a variety of organizations, and it is hoped that this report will serve as a stimulus for such long-term collaborative efforts.

Overview

Papillomaviruses are members of the papovaviridae family of DNA viruses, all of which are considered tumor viruses because of their ability to immortalize normal cells. They are species-specific and occur in a wide variety of vertebrates, where they cause benign and malignant epithelial proliferations. Because papillomaviruses complete their life cycle only in fully differentiated epithelial cells, they are difficult to propagate in cell culture, which has limited the study of their life cycle, immunology, transmission dynamics, diagnosis, and therapy. The initial lack of well-characterized viral antigens also means that, in contrast to most other viruses, papillomavirus taxonomy is based on DNA homology rather than antigenic diversity^{3, 4}. For HPV, more than 100 different types have been detected, over 80 of which have been well-characterized by genomic sequencing, with different types defined as having < 90% homology with DNA sequences of L1 (HPV Nomenclature Committee, 16th International Papillomavirus Conference, Quebec, 1998). Approximately 30 types cause infection of genital mucosal sites, and these genital types are generally characterized as “high-risk” types (e.g., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52), which are associated with low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) and invasive cancer, and “low-risk” types (e.g., HPV 6, 11, 42, 43, 44), which are primarily associated with genital warts, LSIL, and recurrent respiratory papillomatosis (RRP)³⁻⁶.

The sequela of genital HPV infection of greatest public health importance is cervical cancer. For over a century, epidemiologic studies have indicated a relationship between cervical cancer and sexual activity, with consistent associations with age of onset of sexual activity, multiple sexual partners, and contact to “high-risk” males, men with multiple partners or prior partners with genital neoplasia⁷⁻¹⁰. During the past 50 years, there have been ongoing attempts to identify a sexually transmitted agent responsible for these observations, and associations can be found with most sexually transmitted bacteria and viruses. Over the last 15 years, however, the central role of HPV in the pathogenesis of cervical cancer has been firmly established. High-risk types of HPV are found in \geq 93% of cervical cancers worldwide, with HPV 16 present in 50% and HPV 18, 31, and 45 in another 30%^{11, 12}, and case-control studies from several areas have demonstrated odds ratios for HPV detection in cervical cancer of 15-46^{6, 13}. Furthermore, high-grade cervical intraepithelial neoplasia precursor lesions (e.g., CIN 2 and 3) have similarly high rates of the same HPV types (5, 6, 13, 14), and prospective studies have demonstrated a plausible temporal relationship, with infection with high-risk HPV types consistently preceding development of CIN 2/3 (13, 15, 16). Finally, the epidemiologic data are supported by laboratory studies demonstrating that high-risk HPV types contain genomic sequences with oncogenic activity, E6 and E7, which are consistently retained and expressed in cancers. Integration of HPV into cellular DNA occurs in the majority of cancers. This event generally disrupts the HPV E2 transcription regulatory gene and enhances stability of HPV mRNA by attaching it to cellular sequences. Either of these events may lead to increased expression of the E6 and E7 proteins. They, in turn, affect cell growth by binding with cellular tumor suppression proteins, E6 with p53 and E7 with the retinoblastoma gene product, causing their inactivation and ultimately the disruption of normal cell cycle control^{3, 6, 17}.

This body of epidemiologic and laboratory data is sufficiently strong that the International Agency for Research on Cancer and the National Institutes of Health have concluded that high-risk genital HPV types act as carcinogens in the development of cervical cancer^{6, 18}. While infection with high-risk types appears to be “necessary” for the development of cervical cancer, it is not “sufficient” in that cancer does not develop in the vast majority of infected women^{6, 18}, raising questions about other possible co-factors, including smoking, hormonal exposure (e.g., multiparity and

prolonged oral contraceptive use), nutritional deficiency, HLA haplotypes, other genital tract infections, and immunodeficiency, especially HIV infection⁶. The data supporting the role of HPV in other anogenital cancers are more limited, although a large proportion of anal, as well as a subset of vulvar, vaginal, and penile cancers are also associated with high-risk HPV^{6, 19-22}.

Because genital HPV infection is not a reportable condition, assessments of its magnitude are derived by extrapolation from epidemiological studies measuring current infection by detection of HPV DNA, with the most sensitive method being the polymerase chain reaction (PCR) technique, and approximating lifetime infection by measuring HPV antibody in serologic assays. While results have varied by population studied and sampling and detection methods used, overall they indicate that among sexually active women, over 50% have been infected with one or more genital HPV types, approximately 15% have evidence of current infection, 50-75% of which is with high-risk types, and 1% have genital warts^{14, 23-26}. These findings are supported by a recent study of incident HPV infection in young women, which documented a 36-month incidence rate of 43%²⁶. Men have been less well-studied, in part because sites and methods of mucosal sampling are less well-standardized. Levels of current infection in men as measured by PCR appear to be similar to women^{14, 27, 28}, while levels of lifetime infection as measured by serum antibody appear to be lower in men, possibly related to gender differences in the development of antibody after infection^{24, 29}. A recent assessment of the magnitude of various STD in the U.S. estimated an annual incidence of genital HPV infection of 5.5 million and a prevalence of current infection (detectable HPV DNA) of 20 million¹. The majority of infections with all types appear to be subclinical, detectable neither by physical exam nor cytology, but only by the use of HPV DNA detection tests^{14, 23}.

The disease burden created by genital HPV infection is high. Worldwide, there are estimated to be 400,000-500,000 cases of cervical cancer per year^{10, 22}. Most cases occur in developing countries without cervical cancer prevention activities; however, even in industrialized countries, where rates have fallen by up to 75% since the introduction of Pap smear screening programs, the disease burden is still considerable^{10, 30}. In the U.S., for example, incidence rates are currently 8.3/100,000, with approximately 14,000 cases and 5000 deaths annually, despite the performance of an estimated 50 million Pap smears per year. In addition, as a result of these screening activities, an estimated 2.5 million Pap smears with low-grade abnormalities (e.g., atypical squamous cells of undetermined significance-ASCUS, atypical glandular cells of undetermined significance-AGUS, and LSIL) and 200,000-300,000 Pap smears with HSIL are detected annually in the U.S. While these lesions cause no clinical morbidity apart from that resulting from treatment, their magnitude is important because of the health care costs they generate^{31, 32}. Despite the absence of prevention programs, the incidence of other HPV-related cancers are 5-10 fold lower than that of cervical cancer³³, with the exception of anal cancer in homosexual men, which was estimated to be 12-35/100,000 prior to the onset of the AIDS epidemic and which may be higher now^{34, 35}. Estimates for genital warts are less precise than those for cancer because of the absence of case reporting and because they often recur after treatment; however, limited data suggest that in the U.S. incidence rates may be as high as 100 per 100,000³⁶ with a prevalence of 1.4 million¹⁴. Finally, estimates for RRP, a disease of both children and adults in which papillomas of the larynx and upper respiratory tract cause hoarseness and respiratory obstruction, are similarly imprecise, with estimated incidence rates of 0.4 to 1.2 per 100,000 children³⁷. Only limited attempts have been made to estimate the annual cost burden of genital HPV infection in the U.S. Existing estimates range from \$1.6 billion to \$6 billion, making genital HPV the second most costly STD after HIV infection; these estimates do not include costs for management of RRP, indirect costs (i.e., lost time and wages), or intangible costs (e.g., emotional pain, anxiety, disrupted relationships)^{31, 38, 39}.

Factors associated with genital HPV infection in women have been evaluated in a large number of cross-sectional studies. Although smoking, pregnancy, and use of oral contraceptives have been variably associated with genital HPV infection, the most consistent predictors have been various

parameters of sexual activity. The lifetime number of sex partners has been associated with both current and lifetime infection in most studies which have addressed this question^{24, 25, 29, 40-44}. However, several reports have emphasized that number of partners in more recent timeframes is even more highly associated with current infection⁴⁵⁻⁴⁹ and that the number of partners of the sex partner(s) is an additional risk factor^{26, 46}. Studies in men are more limited, but they suggest similar associations with sexual activity^{24, 29, 50}. While non-sexual routes of transmission of genital HPV infection via fomites, non-sexual contact, or vertical transmission are plausible⁵¹ and supported by some but not all serological studies in children⁵²⁻⁵⁴, cervical HPV infection has been rarely detected in virginal females⁵⁵⁻⁵⁷, and it is generally accepted that most genital HPV infections are transmitted by sexual activity^{7, 14}. Alternatively, the likely mode of transmission for RRP is upper respiratory tract exposure to infected genital mucosa, at the time of delivery in juvenile-onset disease and presumably through oral-genital sexual contact for adults⁵⁸.

Of importance, an increasing body of data suggests that the majority of type-specific genital HPV infections are only transiently detectable by DNA detection techniques. Most studies have noted an inverse relationship of age with infection as measured by detection of HPV DNA. Peak rates are found in women ≤ 25 years old, which is speculated to result from clearance of infection over time in most women as an effective immunologic response is induced^{7, 14, 26, 45-48, 59-61}. Although questions remain as to whether HPV infection which becomes non-detectable by PCR has completely resolved or may intermittently reactivate⁶²⁻⁶⁴, median duration of incident infection is reported to be 8 months, with rates of persistence of only 30% after 1 year and 9% after 2 years²⁶. Because women with persistent infection, especially those with high-risk types, are at greater risk for developing CIN^{15, 26, 40, 65} and CIN lesions which persist rather than regress¹⁶, defining determinants of persistence is important in assessing which of the many women with HPV infection are at most risk of subsequent sequelae. Studies to date suggest that infection with high-risk and multiple types of HPV and older age are associated with persistent infection^{26, 66}.

Recommendations From The Workgroups

1. Role of HPV testing in cervical cancer screening

Background

With the recognition of the etiologic role of high-risk types of genital HPV infection in cervical cancer, there has been an intense focus on the use of HPV diagnostic tests in cervical cancer prevention activities. Interest has focused primarily in three areas: triage of women with low-grade Pap smear abnormalities, primary screening, and follow-up of women with confirmed CIN. All three uses are based upon the association of high-risk HPV types with high-grade precursor lesions. Evaluations of these strategies have used both non-amplified and PCR-based testing, although the recent development and FDA approval of a more sensitive signal amplification assay, Hybrid Capture II (HC-II, Digene), should enhance standardized evaluation of these strategies and make reproducible use in clinical settings more feasible.

The most comprehensively evaluated area is HPV testing for triage of low-grade Pap smear abnormalities (e.g., ASCUS, AGUS, and LSIL). Although the majority of women with these cytologic findings have normal histology or lesions which are likely to regress (CIN 1), a minority (5-20%) will have CIN2/3, representing the majority of high-grade lesions in some settings⁶⁷⁻⁶⁹. Current management recommendations for women with low-grade abnormalities offer several options, including follow-up Pap smear evaluation with colposcopy only for those with persistent abnormalities or immediate colposcopy for all women³¹. Neither approach is ideal. Routine colposcopy is costly and generates a large number of unnecessary procedures, while the follow-up Pap smear approach may result in women being lost to follow-up and lower cost-effectiveness, and both approaches may produce anxiety pending completion of the evaluation^{31, 70-72}.

A third option, HPV testing with colposcopy only for those with high-risk types identified, has also been recommended “for physicians who understand its limitations”³¹, but has not been widely accepted⁷²⁻⁷⁶ because of variation of earlier generations of commercially available tests in sensitivity for detection of CIN2/3 (56-93%) and cost-effectiveness^{71, 77, 78}. The current generation HC-II test has an expanded number of high-risk HPV types and a lower detection threshold for HPV DNA, giving it a level of sensitivity similar to that of PCR⁷⁹. It uses a battery of probes to detect presence of *any* of a group of 13 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and *any* of a group of low-risk types (6, 11, 42, 43, 44); it does not allow identification of specific HPV types. Published reports of its performance^{67, 80}, including the largest evaluation to date of HPV testing for triage⁶⁷, demonstrate high sensitivity (approximately 90%) and acceptable specificity (40-65%) for detection of CIN2/3 for women with ASCUS; similar results have been found in women with AGUS⁶⁸. Test specificity and positive predictive value for detecting CIN2/3 are lower in settings where the prevalence of HPV infection is higher, such as younger women or those with LSIL⁸¹⁻⁸³. The strategy of obtaining a sample at the time of the initial Pap smear to save for possible HPV testing is feasible using either liquid-based cytology media (PreservCyt fluid, Cytyc Corporation) or a vial of sample transport media specific for HPV testing. This allows “reflex HPV testing” (testing only the samples from women whose Pap smears are found to be abnormal) without a return visit^{67, 83, 84}, although does require appropriate sample collection and storage procedures. The use of HPV testing for triage is being further evaluated in two large ongoing randomized trials in the U.S. and the U.K. which are comparing the three management strategies and which should provide even more information on their relative clinical value^{70, 85}. Because HPV testing for triage largely serves to

enhance cost-effectiveness of care and reduce patient anxiety^{70, 72}, these RCTs will include cost-effectiveness analyses to complement those currently underway⁶⁷. Potential anxiety generated by HPV testing (when a patient and her partner are told they have or have been exposed to an incurable STD) will need to be considered in both clinical use and cost-effectiveness analyses^{70, 72}.

HPV testing for primary cancer screening is a more complex issue, but one with potentially greater benefit. Used as an adjunct to the Pap smear, it has the potential of increasing sensitivity and specificity of primary screening, and, more importantly, enhancing cost-effectiveness by lengthening the screening interval and determining when screening can be stopped altogether, especially among older women^{70, 77, 86-88}. Of even greater importance is the possibility that it could be an alternative to the Pap smear for accessing women not currently being reached by Pap smear screening. In developed countries, ease of collection via vaginal swab could facilitate screening in clinic settings where pelvic examinations are not routinely available or acceptable or in non-clinic-based settings by outreach workers⁷⁰. In developing countries without Pap smear screening programs, intermittent or even once in a lifetime HPV testing might be more feasible and cost-effective than cytologic screening^{77, 89}, although would require implementation of treatment programs for its benefit to be fully realized. By enhancing population coverage, both of these strategies could not only enhance cost-effectiveness, but also lead to a reduction in cervical cancer incidence and mortality^{77, 89}. In the context of primary screening, several studies have reported enhanced sensitivity for detection of CIN2/3 when HPV testing is combined with cytology in comparison to cytology alone^{90, 91}. There are a number of ongoing studies of primary screening in developed and developing countries comparing cytology, HPV testing, or both for detection of CIN 2/3, with several preliminary reports describing sensitivities of HC-II of $\geq 85\%$ ⁹²⁻⁹⁵. These and other studies, especially those from ongoing RCTs⁸⁷, should provide the additional data regarding positive and negative predictive value and optimal age for HPV testing needed to determine its value in primary screening⁷¹.

Lastly, regarding the use of HPV testing to manage women with confirmed CIN, interest stems from natural history studies which indicate that persistent high-risk HPV infection predicts subsequent development of CIN 2/3^{15, 65, 96-99}, and from studies of women with treated CIN which indicate that persistent HPV is associated with recurrent CIN. Because the large majority of CIN 1 lesions regress without treatment, their routine treatment is not recommended, although close follow-up is required when treatment is deferred^{74, 100}. Determination of whether high-risk HPV types are present, and if so, whether they persist, may help select a group in whom closer follow-up and/or treatment may be most useful. Likewise, following ablative treatment of CIN, approximately 10-15% of women will experience a recurrence^{81, 101}. Presence of high-risk types of HPV DNA is associated with recurrences, and follow-up HPV testing could enhance identification of those most likely to recur, allowing more intensive follow-up^{71, 102-104}.

Workgroup Discussion

The workgroup felt that while the ongoing large RCTs evaluating HPV testing for triage would provide the most useful data from which to make definitive recommendations about the relative value of the three management options, recent data on the performance of HC-II in the triage of women with ASCUS (and AGUS) supported its value in this setting. The workgroup also thought that there are insufficient data to recommend HPV testing routinely for other clinical purposes at present, although there was agreement that testing might be of great value in primary screening and other clinical settings and that studies evaluating these possibilities were priorities. It was noted that although there are no data to address the possibility that CIN 2/3 lesions presenting with ASCUS or LSIL cytology have a different (less aggressive) natural history than those presenting with HSIL, this possibility may influence the cost-effectiveness of HPV testing for triage of low-grade abnormalities. The ongoing RCTs should provide some insight into this question, which may also be amenable to

evaluation by studies of molecular markers in tissues (e.g., specific HPV type, copy number, physical state and transcriptional activity, as well as other markers as they are discovered).

Recommendations for public health/prevention activities

- a. The potential usefulness of HPV testing as an option in the triage of women with ASCUS and AGUS Pap smears should be acknowledged by CDC and other organizations. Formal recommendations about the use of HPV testing in this setting should be made after ongoing RCTs have been completed. HPV testing for other purposes is not currently recommended.
- b. CDC, ACS, and/or other organizations interested in prevention of genital HPV infection and sequelae should facilitate a meeting to review cervical cancer prevention modeling and assess cost-effectiveness of different strategies. This meeting could contribute to interchange of ideas regarding different approaches and development of a unified model and of common instruments to collect data for model calibration to enhance consistency of modeling efforts. The meeting should also attempt to develop and distribute simple cost-effectiveness modules for use by local programs.

Research/evaluation priorities

- a. Demonstration projects should be initiated to evaluate feasibility and cost-effectiveness of HPV testing for triage of ASCUS Pap smears in various “real-world” settings. Such analyses should consider direct costs of providing counseling and education for patients who test HPV-positive and their partners, as well as indirect costs (e.g., lost wages and productivity) and intangible costs (e.g., anxiety, psychosocial burden of being diagnosed with HPV infection). (High priority)
- b. If ongoing RCTs confirm that HPV testing improves clinical management of women with ASCUS Pap smears, focused studies should be performed among high-risk women who may not be adequately represented in multicenter trials (e.g., STD and family planning clinics, minority populations, HIV+ women, adolescents, older women). (High priority)
- c. Additional studies should be performed in U.S. populations to evaluate HPV testing as an adjunct to the Pap smear in primary screening for cervical cancer as a method of enhancing sensitivity and lengthening screening intervals. These should involve evaluation of self-collected samples for HPV testing as a means of increasing coverage of screening programs in difficult-to-access populations and should be supplemented by modeling studies to assess cost-effectiveness. (High priority)
- d. Studies should be performed to evaluate HPV testing as a potentially cheaper and easier to implement alternative to cytology in developing countries that presently lack comprehensive cervical cancer screening programs. (High priority)
- e. Studies should be performed to assess clinical utility of HPV testing in follow-up of women with untreated CIN 1 (i.e., more intensive follow-up and/or earlier treatment for those with persistent high-risk HPV infection) and following treatment of HSIL (as a test-of-cure). (Intermediate priority)

2. Cervical cancer screening in adolescents

Background

Since the early 1980s, U.S. guidelines for cervical cancer prevention have recommended initiating Pap smear screening at age 18 or with the onset of sexual activity^{74, 105-107}. In contrast, because the latency period of cervical cancer after onset of sexual activity is lengthy and rates of cervical cancer are very low in adolescents³³, guidelines in various European countries recommend starting routine screening between the ages of 20 and 30 years. There are several arguments in favor of beginning screening in adolescence. Despite low cancer rates, there are indications that increasing sexual activity in adolescents has resulted in increased rates of CIN^{108, 109}. There is also evidence that the incidence of cervical cancer has increased in younger women (<35 years old) in some countries^{108, 110-112}, although the trend in the U.S. is less clear^{33, 113}. Additionally, questions remain about a possibly increased risk in younger women of “rapidly progressive” lesions which can evolve over a much shorter time than the usual latency period^{114, 115}. Finally, there are concerns that HPV transmission to pre-adolescents as a result of sexual activity or abuse could be underestimated and represent an important problem^{57, 116, 117}.

On the other hand, initiating screening at such a young age raises several problems^{116, 118-121}. First, screening in adolescents is likely to be less cost-effective than in older women, both because the development of high-grade lesions within the first several years after the onset of intercourse is infrequent and because the latency period of those which do occur is generally long enough to allow their detection if screening is initiated in the early-mid 20s^{30, 107}. Furthermore, modeling studies suggest that CIN has a higher probability of regression in younger than older women¹²², which is likely a result of higher rates of recently acquired genital HPV infection in young women, whose manifestations are usually transient, in contrast to the greater likelihood of persistent infection in older women. These considerations suggest a greater potential for detecting transient low-grade abnormalities in younger women, which lead to additional unnecessary management costs^{89, 118, 122}. Second, there are concerns that adolescents may have a higher rate of post-treatment complications than older women, both physiologic and behavioral. Although the data regarding long-term effects of the therapeutic modalities for CIN in current widespread use (e.g., cryosurgery, LEEP, and laser) do not suggest an increase in problems related to fertility or pregnancy, the studies have had relatively short follow-up periods and have been too small to evaluate age-specific outcomes¹²³. One recent report of complications of cryosurgery in adolescents reported PID in 9%, cervical stenosis in 3%, and cervical narrowing in 30%¹²⁴. It has also been suggested that the anxiety engendered as a result of undergoing a pelvic exam or of being informed of a “pre-cancerous” Pap smear result may be greater in adolescents than in older women^{118, 119}.

Workgroup discussion

The workgroup agreed that several questions were important to address regarding Pap smear screening of adolescents. It was not felt that current recommendations about age of onset of screening should be changed. However, because of the likelihood of a more benign natural history of CIN 2/3 lesions and limited data on long-term complications in younger women, the workgroup felt that screening in adolescents may have low cost-effectiveness and thus bears reconsideration. There was consensus that it would be useful and ethical to learn more about the natural history of CIN 2 lesions in adolescent women and that, in young women in whom follow-up could be assured, it would be appropriate to follow such lesions without treatment in research settings. In those undergoing both Pap smear and STD testing, it was felt that bleeding induced by cervical swabs was potentially a greater problem for cytology than for cervical gonorrhea or chlamydia tests and that the Pap smear should be collected first.

Recommendations for public health/prevention activities

- a. Because the large majority of cervical lesions in adolescents are self-limited, in those with low-grade cytologic abnormalities (e.g., ASCUS, LSIL) consideration should be given to conservative follow-up by repeat Pap smear rather than triage by HPV testing (since predictive value in adolescents is not well-characterized) or by early colposcopy/biopsy.
- b. CDC and ACS should recommend that the cytology sample be collected first when Pap smear screening is conducted simultaneously with STD testing. If STD tests are run on single samples collected as part of liquid-based cytology testing, sequence questions will not be an issue.

Research/evaluation priorities

- a. Prospective studies of the natural history of untreated CIN 2 in adolescents should be performed in carefully monitored research settings. Although similar natural history studies of untreated CIN 3/CIS would be difficult to perform for ethical reasons, comparative molecular studies (e.g., specific HPV type, copy number, physical state and transcriptional activity, as well as other markers as they are discovered) of these lesions in younger versus older women would be useful in assessing possible differences in natural history. (High priority)
- b. Studies should be performed to better characterize the incidence and type of long-term reproductive complications of ablative therapy of CIN in adolescents. (High priority)
- c. Studies should be conducted to determine if the experience of undergoing ablative therapy of CIN influences future health-care seeking behavior of adolescents (e.g., makes them less likely to return for follow-up to avoid pain or complications). (Intermediate priority)
- d. Studies should be conducted to determine the feasibility of recommending initiation of Pap smear screening a certain number of years after acknowledged first sexual activity rather than at a specific age (e.g., determine rate of abnormality by years of stated activity, willingness to discuss age of onset of sexual activity). (Intermediate priority)
- e. Multicenter studies should be performed comparing younger and older women with invasive cervical cancer to determine whether rapid onset disease is more common in younger women and, if so, to assess associated risk factors (e.g., HPV type, histologic type, age of onset of sexual activity, presence of other co-factors). (Low priority)

3. Non-vaccine modalities for primary prevention of genital HPV infection

Background

The reproductive rate of a sexually transmitted infection in a susceptible population is a function of three parameters: the efficiency of transmission per sexual partnership, the duration of infectivity, and the number of new partners an infected person has per unit of time^{125, 126}. In the absence of measures to reduce susceptibility (e.g., effective vaccines), strategies to reduce each of these parameters can reduce transmission of infection: the efficiency of transmission by strategies to reduce infectivity (e.g., condoms, microbicides), the duration of infectivity by treatment, and new partnerships by behavior change approaches. There is limited understanding about the value of each of these approaches for prevention of genital HPV infection.

Theoretically, barrier contraceptives such as condoms are less likely to be effective in preventing infections such as genital HPV, which can involve the external genital skin, than they are for infections which are limited to specific mucosal areas and spread by semen (e.g., chlamydia or gonorrhoea), although estimation of potential benefit of condoms for HPV is hindered by absence of measures of infectivity. Studies which have attempted to assess male condom benefit for women have generally found no evidence of protection against infection^{26, 28, 43, 45, 46}. However, existing reports have not adequately assessed consistency and correctness of condom use, and, in cross-sectional studies, HPV infection may have preceded condom use. There are data suggesting a benefit of condom use for men, although the studies are limited^{29, 50} and no data available for female condoms for either women or men. Some reports have suggested a benefit in prevention of HPV-related disease (e.g., genital warts, SIL, cervical cancer)^{50, 127-130}, possibly by reducing viral inoculum, repeated viral exposure, or exposure to other co-factors which might be involved in development of disease. However, a protective effect has not been seen consistently^{131, 132}, and the cross-sectional and case control studies published to date are limited by recall bias and the difficulty in controlling for a variety of important variables^{132, 133}.

There are also reports of a potential protective effect of spermicides in the prevention of cervical cancer^{127, 128, 131, 132}, which is of interest because of the microbicidal properties of such agents¹³⁴. Evaluation of the activity of microbicides has been hampered by the difficulties with *in vitro* cultivation of HPV, which is needed to screen potential products. However, recent work with various papillomaviruses in animal systems indicates that while nonoxynol-9, which functions largely as a detergent that disrupts lipid envelopes, has no activity against non-enveloped viruses like papillomaviruses, other agents such as povidone-iodine and the detergent sodium dodecyl sulfate (SDS), which also denatures proteins, inactivate papillomaviruses including HPV¹³⁵⁻¹³⁷. Since SDS is a common ingredient in toothpaste and shampoo, it may be a promising agent for clinical trial evaluation in the future should human toxicity studies indicate lack of mucosal irritation with prolonged use.

In contrast to bacterial STD, for which transmission can be prevented through curative treatment, there is no evidence that treatment of HPV-associated lesions is useful in prevention of transmission. There are no effective systemic therapies for genital HPV, as there are for bacterial and other viral STD, and current treatment options include a variety of locally destructive approaches for both genital warts and SIL, as well as topical use of cytotoxic and immunomodulating agents for genital warts¹³⁸. It has been speculated that treatment of genital warts might be useful in reducing infectiousness¹³⁸. This premise is difficult to test because of the lack of assays for infectivity, but is supported by observations that treatment of genital warts with the immunomodulating agent imiquimod reduces viral DNA and mRNA in post-treatment biopsies¹³⁹ and that therapy of CIN results in clearance of HPV in follow-up cervical swabs in 70-80% of women^{102, 104}. However, clinically normal skin and mucosa in the vicinity of HPV-associated lesions often contain HPV^{140, 141}. This reservoir is thought to explain the typical recurrence rates of 10-20% after treatment for CIN^{81, 103} and 20-50% after treatment of genital warts¹⁴² and the fact that treatment of partners does not influence recurrence rates of genital warts¹⁴³. Thus, based on limited existing data, currently available therapies for HPV-related lesions may reduce but probably do not eliminate infectiousness, and whether the reduction in viral load which occurs with treatment impacts future transmission remains unclear.

Workgroup discussion

The workgroup agreed that existing data were not supportive of a benefit of male condoms, especially for women, but that because existing studies had serious methodologic limitations, an RCT would be the only study design by which the issue could be clarified. However, such a trial would be difficult and expensive to conduct, and because of the low probability of documenting benefit, a trial

specifically designed to evaluate the value of condoms for HPV prevention would not be a high priority. A more efficient approach would be to include HPV outcomes in prevention trials being undertaken for prevention of HIV or other STD, in which use of condoms or microbicides could be carefully documented. There was also agreement that comparison of the efficacy of existing treatments for genital warts, development of new therapies for genital warts and CIN, and a better understanding of the impact of existing and new therapies on transmission were important issues.

Finally, there was extensive discussion about the merits of trying to reduce genital HPV transmission by focusing on behavior change approaches. As noted, the most consistent risk factor for HPV prevalence in cross-sectional studies and HPV incidence in observational studies is number of partners and, secondarily, partners' number of partners^{25, 28, 29, 40-49}. It was pointed out that although HPV-related mortality is at least twice that of HIV for women in the U.S., the predominant STD/HIV prevention messages promoted are those pertaining to HIV risk reduction, and that, in contrast to HIV¹⁴⁴, no attempts have been made to look at benefit of counseling strategies for HPV prevention. Since most women and men do not understand the prevalence of genital HPV infection or its role in cervical cancer, such knowledge might give them reasons to modify behavior. Increased awareness that HPV infection is widespread, that it might not be fully prevented by condom use, and that it can have rare but serious sequelae might help stimulate and sustain efforts to reduce exposure to HPV and other STD. Such strategies could include delay in initiation of sexual intercourse, a reduction in the number of partners, and selection of partners perceived to have had fewer partners.

Options for prevention trials to evaluate the benefit of a behavior change approach could include individualized counseling or health education messages delivered at the community level, with a focus on the magnitude of genital HPV infection, its association with cancer, and the benefit of reducing partners and selecting less sexually experienced partners. However, concern was expressed that, although an intuitively promising approach, such a strategy would have a number of potential problems, including stigmatization and exaggerated fear about what would likely continue to be a very common STD, difficulty in using this approach for the large number of women in the population with very few sex partners¹⁴⁵, a likely increased emphasis on and requests for HPV tests, whose meaning would be difficult to interpret, and a potential to undermine condom use, possibly enhancing acquisition of other STD (e.g., HIV, gonorrhea) which are more effectively prevented by condom use.

Recommendations for public health/prevention activities

- a. Given the uncertainties about prevention of transmission of genital HPV to sexual partners, promulgation of a "standard script" for providers to use in education/counseling of patients with HPV infection (e.g., genital warts or CIN) would be helpful. Key messages should include the following:
 - Persons with genital warts or CIN should be informed about the high prevalence of HPV infection among adults who have been sexually active and the likely persistence of infection after treatment for an indefinite period of time.
 - Those with monogamous partners should be counseled that partners may already have been infected.
 - No scientific data support condom use specifically for genital HPV prevention; however, condoms should be recommended for prevention of other STDs.
 - Because duration of infectiousness is unknown and because genital HPV is so common among persons who have been sexually active, the value of disclosing a past diagnosis of HPV infection to future sex partners is unclear, although candid discussions about past STD should be attempted whenever possible.

- Given the complexity of counseling messages, clinicians should be encouraged to refer patients to educational materials, hotlines, and other appropriate resources.

Research/evaluation priorities

- a. Randomized clinical trials designed specifically to assess prevention of genital HPV infection by male and female condoms in both women and men would be desirable; however, these will be difficult and expensive to perform. Thus, attempts should be made to include HPV outcomes (e.g., incident infection defined by HPV DNA detection in mucosal samples or by seroconversion; development of cervical SIL lesions) in ongoing/planned RCTs of various primary prevention modalities (e.g., condoms, microbicides, behavior change) for prevention of HIV and /or other STD. (High priority)
- b. Because of the limited confidence in condoms for prevention of genital HPV infection, studies of behavior change (e.g., reduction in number of partners, selection of less sexually experienced partners, and delayed onset of intercourse, and which focus in part on the high prevalence and relative difficulty of preventing HPV infection) to prevent HPV outcomes should be considered. Although it was recognized that such studies would be difficult to perform and could have the unintended consequence of increasing the stigma and anxiety associated with HPV infection, they could also have other STD prevention benefits. These studies would also need to address the potential of such behavior change approaches to undermine condom use, possibly enhancing acquisition of STD (e.g., HIV, gonorrhea) more effectively prevented by condom use. (High priority)
- c. Additional studies of the role of treatment in preventing transmission should be performed including assessment of persistence of detectable HPV DNA after treatment of GW and SIL. (Intermediate priority)
- d. In order to inform patient counseling (especially as HPV testing becomes more common), transmission modelling, and intervention assessment/planning, studies to better define laboratory markers of genital HPV infectivity (e.g., viral load, mRNA detection, viral capsid protein detection, etc.) in different anatomic sites and lesion types should be performed. (Intermediate priority)
- e. Additional studies of risk factors of persistent HPV infection should be performed because of the potential role of persistent infection in transmission dynamics in women and men, as well as in predicting subsequent neoplasia. (Intermediate priority).

4. Preparedness for prophylactic HPV vaccines

Background

The difficulty with non-vaccine modalities of primary prevention and the large global burden of HPV-related disease make the development of effective prophylactic vaccines an important public health priority³². Initial barriers to development of promising candidate HPV vaccines included the difficulties in propagating the virus in vitro, the potential hazard of a vaccine containing an oncogenic viral genome, and the lack of an animal model of HPV infection suitable for challenge experiments^{32, 146-148}. The development of L1 virus-like particle (VLP) subunit vaccines through molecular biologic techniques has remedied the first two problems. L1, the major capsid protein and the site of the primary neutralizing epitopes of HPV, self-assembles into particles resembling authentic virions after expression in eukaryotic cells, thus retaining the native conformation required for induction of neutralizing antibody. The lack of an animal model for studying HPV

remains an issue, although challenge studies with species-specific papillomaviruses and parenteral injection of VLPs have demonstrated a consistently high level of protection (90-100%) against infection in three animal systems, one cutaneous (cottontail rabbit PV) and two oral mucosal (bovine PV type 4 and canine oral PV)¹⁴⁶. These results have stimulated great enthusiasm about the potential of VLP vaccines to prevent infection in humans. Several Phase I trials sponsored by industry and by the NIH with monovalent HPV 6, 11, and 16 VLP vaccines are underway, with subsequent larger clinical trials likely if the initially promising immunogenicity and safety results are confirmed^{32, 147}.

Although there is cause for optimism about the potential value of VLPs as prophylactic HPV vaccines, several important issues remain to be addressed. First, the animal challenge studies, although encouraging, have not used natural routes of mucosal infection, and vaccination strategies which produce greater levels of mucosal immunity may ultimately be required to prevent human infection. Second, while trials of monovalent vaccines are appropriate for initial proof of concept studies, polyvalent vaccines will ultimately be preferable because of the large number of HPV types found in cervical cancer and genital warts and the apparent lack of cross-type immunity produced by L1 vaccines, adding to the time required for full evaluation. Third, cervical cancer will not be a feasible endpoint to study because of its long latency, and clinical trials will need to focus on shorter-term (and more indirect for cancer prevention) measures such as HPV infection and CIN. Fourth, initial studies will need to be conducted in females in order to assess CIN outcomes and while studying those without prior genital HPV exposure is desirable, trials may need to focus on young adults rather than adolescents for ethical reasons. This presents an issue of translating clinical trials into practice, since the ideal target for an STD with a high incidence soon after onset of sexual activity would be pre-sexually active adolescents or children, including males as well as females. Ultimately, a vaccine which has therapeutic value in early infection as well as prophylactic value would be optimal, providing benefit to those who are already infected as well as those uninfected; this may allow a greater flexibility of populations who could be targeted, and thus possibly earlier public health benefit in terms of cancer prevention^{32, 147, 148}.

Workgroup discussion

Effective HPV vaccines would represent a major public health advance and their development was strongly endorsed by experts across multiple disciplines as a high priority research initiative. The workgroup participants thought that industry and the NIH should continue to play the primary role in developing new candidate vaccines and assessing their efficacy in clinical trials. In addition, there are a number of important issues which will need to be addressed both prior to as well as following licensure of effective vaccines which might appropriately involve CDC or other organizations interested in prevention of genital HPV infection. Several issues were felt to be important for upcoming clinical trials. Of immediate concern was a better understanding of the incidence and natural history of HPV infection in men, since they will likely be included in clinical trials at some point. Also, because serologic measures of incident infection are insensitive and, after VLP immunization, nonspecific for natural infection versus vaccine response, another priority of relevance for clinical trials is development of cheaper and less intrusive methods to establish incident HPV infection through samples collected from mucosal surfaces in order to permit less costly and more frequent assessment of outcomes. Additional issues would become important if initial trials indicated the likelihood of vaccine efficacy. For example, because cost analyses have been important in driving other vaccine implementation efforts and also in influencing pricing decisions, cost-effectiveness studies of vaccines for both high-risk and low-risk types of HPV would be useful and could lead to collection of specific cost data during final trials in order to refine analyses. Also, transmission modeling studies could help assess the level of vaccine efficacy required for a population-based benefit¹⁴⁹ and could also be of value in assessing different age and gender mixes in vaccine implementation strategies. Of particular concern are issues of gaining acceptance among the general

public and healthcare providers for an HPV vaccine. The experience with hepatitis B immunization, the only STD for which an effective vaccine exists, showed that implementation was limited in the general population until a universal immunization approach was recommended, and even with hepatitis B, because of other routes of transmission, the “STD connection” has not been emphasized. The workgroup felt that effective ways of presenting an HPV vaccine to the public, including parents who would need to consent if the vaccine were administered to minors not yet sexually active, and also to providers need to be explored, preferably in collaboration with industry. These assessments should include whether the vaccine is best described as one to prevent a common STD, which would be applicable to both females and males, versus a vaccine to prevent cancer, which would be largely relevant for females.

Research/evaluation priorities

- a. More extensive population-based studies should be performed of rates and risk factors for genital and anal HPV incidence, prevalence, and persistence in men. These studies should include adolescent and young adult heterosexuals as well as men who have sex with men (MSM) and should be conducted in both developed and developing countries. (High priority)
- b. Improved sampling and testing methods are needed to detect incident genital HPV infection as a study outcome, including assays sensitive enough to detect HPV infections in men, sensitive and specific methods to detect type-specific (and quantitative) HPV infection, and methods amenable to self-sampling (to allow more frequent and less expensive measurements of outcomes). (High priority)
- c. Given that there is no experience with implementing immunization programs for infections transmitted predominantly by sexual activity, marketing research about HPV vaccine acceptability in adolescents, their parents, and their health care providers should be encouraged by and/or carried out by CDC. (High priority)
- d. Mathematical modeling studies of genital HPV transmission should be performed in order to assess optimal targets for immunization programs (e.g., age and gender mix). (High priority)
- e. Cost-effectiveness studies of HPV vaccines should be carried out from a societal perspective, including assessment of indirect and intangible costs. These should include studies of HPV 6/11 to further encourage industry efforts to develop and test vaccines for these types, both as a means of preventing their sequelae (e.g., genital warts, CIN 1, and recurrent respiratory papillomatosis) in women as well as to offer benefit to men. (High priority)
- f. Studies of alternative, potentially more convenient routes of delivery and dosing schedules of HPV vaccines should be conducted. (High priority)
- g. Following successful efficacy trials of HPV vaccines in young adult women, immunogenicity studies should be performed in other populations (e.g., heterosexual men and MSM, young adolescent men and women, higher risk patients such as those attending STD clinics). (High priority)
- h. Following licensure of an effective vaccine, studies should be performed to assess behavioral implications of its use (e.g., increases in risky sexual behavior due to misperceptions about vaccine protection against other STD, reduced compliance with cancer screening recommendations, etc.). (Intermediate priority)

5. Provider, patient, and public awareness

Background

Improvement in awareness by health care providers and the general public has been an important strategy in response to widespread public health problems such as HIV infection. Greater provider understanding can improve management of patients and provision of information to them and their families (or partners in the case of STD), and awareness in the general public can enhance responsiveness to prevention activities, such as screening or immunization. Data on provider understanding about genital HPV infection are limited. They suggest that providers are broadly aware of the sexually transmitted nature of the infection and its relationship to cervical cancer, but are less clear about the relationship of genital warts to cancer, the indication for use of various management strategies, transmission-related issues, and the indications for partner evaluation¹⁵⁰⁻¹⁵². This lack of clarity, coupled with discomfort over discussion of issues related to STD and sexuality and limited time for counseling/education, is often perceived by patients as inadequate information and advice¹⁵²⁻¹⁵⁴. Limited data from selected populations show substantial levels of emotional distress among patients with a diagnosis of genital HPV infection (genital warts or abnormal Pap smears), which can far exceed the level of physical distress. These include feelings of shock, shame, anger at partners and providers, depression, and fear about sequelae and ongoing contagiousness^{152, 153, 155-157}. Fear of or actual experience of rejection in future sexual relationships was reported by 67% and 19% of patients, respectively¹⁵³.

Workgroup discussion

The workgroup felt that the awareness of cervical cancer and of Pap smear screening as a prevention strategy are widely recognized and supported by the general public in the U.S. However, the linkage of genital HPV infection to cervical cancer is much less widely recognized, and understanding of genital HPV as an STD is limited, with STD awareness only slightly greater among women with multiple partners than other women¹⁵⁴. Promoting public awareness in these areas is appealing, but represents a complex situation. On the one hand, a policy of consistently informing the public about strongly documented scientific findings is likely to be the most ethical and effective policy in the long run, and may help to lessen stigma and increase sympathy for persons suffering from sequelae of STDs. Such messages could also be useful in enhancing future acceptance of HPV immunization programs³². Furthermore, STD prevention messages that have been underutilized to date because of concerns over their likely benefit (e.g., reducing the number of sex partners and choosing safer sex partners) might become more acceptable strategies for many individuals if there were greater awareness of the magnitude of genital HPV infection.

On the other hand, promotion of greater awareness that cervical cancer is linked to an STD could conceivably undermine general support for Pap smear screening programs or could lead women or providers to decide that a woman considered to be at low risk for an STD does not need a Pap smear. Directing prevention messages to the general public is further complicated by the lack of clarity of what the most appropriate health care and prevention strategies are for HPV infection, given that most infected persons are asymptomatic, the overwhelming majority will not suffer any adverse consequences, no data document that condoms are effective for HPV prevention, diagnostic services are relatively expensive, and diagnosis of HPV infection has not yet been demonstrated to lead to improvement in health outcomes. Therefore, it may be counterproductive to promote messages that increase anxiety in the absence of effective strategies to reduce risk for infection. The workgroup emphasized that messages must be carefully crafted to deal with these complexities and that assessment of such prevention messages should be a critical element of research. Audiences must at least be segmented into providers, persons with known HPV infection, and the general

population. When messages are directed to patients or to the general public, it is important that parallel efforts be made to inform providers at same time.

Provider awareness

Recommendations for public health/prevention activities

CDC, ACS, and other organizations interested in prevention of genital HPV infection and sequelae should draft a consensus statement for use in professional educational materials of what has been scientifically established about HPV (as well as what is not known). This statement should address currently available diagnostic, treatment, prevention, and counseling/education strategies and should be widely disseminated (e.g., published, put on websites, etc) and updated on a regular basis.

Research/evaluation priorities

Although methodologically challenging, surveys of provider knowledge, attitudes, and practices should be conducted to guide future targeting of educational efforts. (Intermediate priority)

Patient awareness

Recommendations for public health/prevention activities

In conjunction with development of professional educational materials, patient educational materials should be developed and distributed widely, and their use and/or adaptation by groups involved in patient education strongly encouraged.

Research/evaluation priorities

- a. Efforts should be made to assess counseling/educational needs for patients (and partners) with HPV-related diagnoses and to develop alternatives to physicians as primary providers of education/counseling. These might include other types of patient educators (e.g., nurse clinicians who provide diabetes education, which is now a billable non-physician service), brochures, web-based material, hotlines, etc. (High priority)
- b. Studies should be performed on the behavioral/psychosocial impact of HPV-related diagnoses on persons with genital warts and CIN and their partners and the impact of disclosure about these conditions on current and future sexual partnerships. (Intermediate priority)

Public awareness

Research/evaluation priorities

- a. Knowledge and attitude surveys should be performed to assess information needs of various populations within the general public and to help guide existing and possible future public awareness activities. (Intermediate priority)
- b. Pilot public education programs should be carried out in selected areas to assess optimal form and content of public awareness messages as well as potential drawbacks (e.g., stigmatization of Pap smear screening programs, competition with other public health prevention messages), both to respond to the increased public concern likely to occur with wider use of HPV testing and also to enhance prevention activities related to HPV and sequelae

(i.e., Pap smear screening, vaccine preparedness, general understanding of relationship of HPV to cervical cancer) . (High priority)

6. Anal Cancer

Background

Anal cancer is a relatively uncommon malignancy, with a current U.S. incidence rate of only 0.9/100,000³³. However, incidence rates are reported to have increased over the past 20-30 years in several countries^{19, 33, 34, 158}, including the U.S., where rates increased by 96% for men and 39% for women from 1973-97³³. This increase has been partly ascribed to changes in sexual activity. There is a growing body of data linking anal cancer to sexual behavior, especially anal intercourse, and HPV infection^{19, 159, 160}. The highest incidence is reported in MSM, with rates 12 to 50 times higher than in heterosexual men¹⁵⁹⁻¹⁶² and an overall annual incidence rate of up to 35/100,000¹⁵⁹, similar to rates of cervical cancer among women in the absence of Pap smear screening¹⁶³. Women with previous cervical cancer are also at higher risk for anal cancer, an association likely attributable to the presence of HPV infection at both sites¹⁶⁴.

An additional factor in this increase may be the HIV epidemic. Prevalence rates of anal SIL (ASIL) of 20-45% have been reported in HIV+ MSM, substantially higher than in HIV- MSM, with ASIL most strongly correlated with HPV infection^{163, 165-168}. Two prospective studies have documented a higher incidence of anal HSIL lesions in HIV+ vs. HIV- men, with incident HSIL associated with persistent HPV infection in both HIV+ and HIV- men^{166, 168}. Finally, rates of anal cancer are estimated to be 30-80 fold higher in patients with AIDS than in the general population, although the proportion of this increase attributable to the higher overall rates seen in MSM versus the effect of HIV-related immunodeficiency has not been determined^{162, 167, 169}. These data have led to consideration of the potential benefit of anal cancer prevention programs^{163, 170, 171} through cytologic screening, since evaluations to date suggest that anal Pap smears may be similar in sensitivity to cervical smears^{172, 173}. This approach is supported by modeling studies of anal cancer screening in MSM, which indicate that the cost-effectiveness of screening could be similar to that for other prevention interventions. However, the models are most sensitive to assumptions about the natural history of anal LSIL, about which there are limited data, and the natural history of HSIL and the effectiveness of ablative therapy, about which there are virtually no data^{35, 174}. Furthermore, little is known about the complications of ablative treatment, either in terms of medical costs or effect on quality of life. An additional consideration is the uncertain impact of the use of highly active antiretroviral therapy in HIV+ MSM, in that it could possibly lead to either an increased risk of anal cancer owing to greater longevity or a reduced risk owing to better control of HPV infection and regression of SIL lesions as a result of improved immune function¹⁷⁵.

Workgroup discussion

Despite the relative infrequency of anal cancer at the population level, the workgroup thought that pursuing prevention strategies for high-risk groups (primarily HIV+ MSM, but also HIV+ women and HIV- MSM) was important, and that studies to obtain better information about natural history and effectiveness of treatment of anal SIL lesions were high priorities. There were differences of opinion on how best to conduct these studies. On the one hand, because so many key questions about a potentially important prevention strategy remain unanswered and because lack of wide-spread implementation of anal cancer screening programs to date mean that “standards of care” have not been established, most of the workgroup felt that it would be ethical and appropriate for these studies to be implemented as RCTs. Such studies could provide much-needed unbiased data on rates of progression and regression of HSIL, and if follow-up were performed at close intervals, could minimize the risk of those anal cancers which did occur developing beyond an early stage.

Likewise, they could provide the best information on the effectiveness and complications associated with ablative therapy. On the other hand, there was also an opinion that, because of the biologically plausible analogy with the cervix and the risk of untreated HSIL progressing to cancer, it would be ethically problematic not to offer therapy to those with such lesions. An alternative evaluation methodology could thus involve a demonstration project of anal cancer screening, with follow-up of those electing no treatment for HSIL to assess natural history and of those choosing treatment to assess efficacy and complications of therapy. This approach would also provide the opportunity to assess operational feasibility and training needs of an anal cancer screening program and help to further refine cost-effectiveness analyses.

Research/evaluation priorities

- a. Multicenter projects (RCTs or demonstration projects) should be initiated to assess parameters of importance in anal cancer screening programs in MSM, especially a better understanding of the natural history of LSIL and HSIL in HIV+ and HIV- MSM and the efficacy and complications of ablative therapy of anal HSIL in HIV+ and HIV- MSM. (High priority)
- b. Studies should be performed to determine reproducibility, interobserver variability, optimal sampling technique, and predictive value of anal Pap smears. (High priority)
- c. Analogous to studies of cervical cancer prevention, studies should be performed to evaluate performance of HPV testing in triage of abnormal anal Pap smears and in primary screening. (Intermediate priority)
- d. Studies should be performed to determine risk factors for women and heterosexual men with anal cancer as a possible guide to future screening programs. (Intermediate priority)

7. Surveillance for genital HPV infection and sequelae

Background

The term “surveillance” in public health encompasses a range of activities. Surveillance for STDs in the U.S. includes three categories of activities: case notification (e.g., reporting of individual cases of notifiable conditions by providers or laboratories), prevalence monitoring (e.g., monitoring the prevalence of infection in settings where screening occurs systematically), and other special studies (e.g., sentinel surveillance activities, supplemental testing which may provide information about the incidence or prevalence of an STD). To avoid unnecessary workloads for providers and laboratories, case notification is recommended for STD with case management implications (e.g., curative treatment, partner notification), with planned or ongoing prevention programs (e.g., screening, immunizations), or in the setting of an outbreak. Case notification of STDs for these purposes is currently recommended nationally by the Council of State and Territorial Epidemiologists (CSTE) only for syphilis, gonorrhea, chlamydia, hepatitis B, and chancroid. All three categories of surveillance activity are reflected in current U.S. surveillance data for STDs¹⁷⁶.

HPV infections and their sequelae pose many challenges for routine public health surveillance efforts. The estimated number of new infections with genital HPV is substantially higher than those of the reportable STD¹, and they are largely undiagnosed given the limitations of routine diagnostics. Although there have been no national recommendations encouraging case notification of HPV infection, a number of states have made genital warts a reportable condition. Preliminary analysis of these reports indicate that they did not provide representative data since the vast number came from public clinics and were of warts in men, despite the widespread occurrence of genital warts in women (DSTD, unpublished observations). Special surveillance studies for genital HPV infection

include assessment through the National Disease and Therapeutic Index (NDTI) of the number and proportion of ambulatory care visits in the U.S. accounted for by genital warts¹⁷⁶, a sentinel surveillance system for RRP³⁷, and a population-based national household survey, the National Health and Nutrition Examination Survey (NHANES), which has provided valuable information about trends in infection with genital herpes¹⁷⁷ and from which pilot seroprevalence surveys for HPV 16 and 6/11 are planned.

At the other end of the natural history spectrum, surveillance for cervical and other anogenital cancers is through cancer registries. National cancer surveillance in the U.S. has been carried out through the NIH National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program since 1973, comprising 11 geographic areas covering about 14% of the U.S. population. Extrapolations from these data are used to determine rates and trends in various types of cancers and are also the basis for annual estimates of cancer incidence compiled by the American Cancer Society. To supplement data collected through SEER on a broader geographic basis, CDC initiated the National Program of Cancer Registries (NPCR) in 1992, which will cover over 95% of the population when fully operational.

Workgroup discussion

The workgroup concluded that at the current time public health surveillance for genital HPV infection is best done through prevalence monitoring and special studies rather than through case reporting, because of the absence of the rationale for such as discussed above. There was discussion about a range of potential new surveillance activities for HPV infection and related sequelae in the U.S., focusing particularly on events in the natural history of HPV infection that are intermediate between first acquisition of infection at one extreme, and diagnosis of cancer at the other extreme. For high-risk HPV types, such events might include: development of persistent genital HPV infection, given its association with development of CIN; detection of serologic evidence of type-specific infection, given its association with persistent mucosal infection²⁵; and detection of cervical carcinoma in situ (CIS). There was consensus that CIS, as the most advanced pre-cancerous precursor lesion, would be extremely useful to follow at a population-based level as an early indicator of the impact of an HPV immunization program. It was noted that since this diagnosis is increasingly made in outpatient settings, it had become difficult to capture through traditional cancer registry programs which focus on hospital-based care, and that because of this problem, the SEER Program had recently chosen to discontinue collection of this diagnosis. Suggestions about alternative systems, albeit not population-based, from which to collect data on rates of CIS include sentinel surveillance within managed care organizations or the Indian Health Service. For low-risk HPV types, key events for surveillance include not only genital warts, which may be possible to track through clinic-based and administrative datasets more effectively than is currently the case through NDTI, but also juvenile-onset RRP, which is as common as neonatal herpes infection but much less widely recognized.

Recommendations for public health/prevention activities

- a. Routine disease reporting (e.g., case notification) of all genital HPV infections or of any specific HPV disease or type (e.g., genital warts, HPV 16 infection) is not practical and thus not recommended at this time.
- b. CDC should conduct further analysis of the experience with genital warts reporting in various states to guide future directions in genital warts surveillance. Although data from the NDTI have limitations, their continued analysis by CDC is recommended until superior data, preferably population-based, become available.

- c. Routine reporting of CIS could represent a valuable adjunct to cancer surveillance, especially as HPV immunization programs are implemented. However, because of past problems encountered by SEER, future efforts to report and interpret data on CIS should examine this experience and consider alternative approaches to monitor this diagnosis.
- d. Surveillance for HPV-related cancers should be enhanced in ways that contribute to understanding the causative role of HPV infections and to prevention strategies. Such enhancements could include recording the sexual preference of men with anogenital cancers (recognizing that this will depend upon the consistency with which this variable is recorded in the medical record).

Research/evaluation priorities

- a. Pilot NHANES seroprevalence studies by CDC should be continued and other subpopulations for similar studies should be identified, since monitoring serologic evidence of infection with HPV 16 and/or other high risk types may be an efficient method of prevalence monitoring. These studies should also be expanded to include self-collected samples such as vaginal swabs and urine samples for HPV DNA studies, with a focus on specific types likely to be included in vaccines, since these may enhance data provided by serologic studies in monitoring levels of type-specific infection over time. (High priority)
- b. A sentinel approach, possibly in areas where other sentinel surveillance activities (e.g., SEER or one of the NPCR sites) have been established, should be considered in order to evaluate the spectrum and trends of HPV-related disease and as a foundation for subsequent population-level prevention activities such as immunization programs. Such activities might include monitoring specific types and type-variants of HPV infection and population-based Pap smear registries. (High priority)
- c. The current CDC sentinel surveillance for juvenile-onset RRP should be strengthened and expanded (e.g., additional sites; more data related to acquisition of infection, including maternal HPV status and other risk factors for mother-child transmission; consideration of case control and/or observational studies to better define risk factors for transmission and potential benefit of interventions such as C-section). (High priority)
- d. Because ICD and CPT codes do not accurately capture HPV-related diagnoses, treatments, or procedures, CDC should explore efforts to redefine these codes. Such changes would enhance prevalence monitoring of HPV-related outcomes and ongoing assessments of HPV-related healthcare costs in large administrative databases (e.g., Medicaid, Medstat, etc.). (Intermediate priority)
- e. CDC should make efforts to collaborate with organizations that have electronic databases of patient encounters which include variables such as reason for visit and primary diagnosis (e.g., STD clinics, group model HMOs, etc.) in order to monitor trends in and assess burden of health care related to the prevalence of genital warts. (Intermediate priority)

REFERENCES

1. Cates W, American Social Health Association Panel. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. *Sex Transm Dis.* 1999;26(suppl):52-57.
2. Lytwyn A, Sellors J. Sexually transmitted human papillomaviruses: current concepts and control issues. *Can J Hum Sex.* 1997;6:113-126.
3. Galloway DA. Biology of Human Papillomaviruses. In: Holmes K, Mardh P, Sparling P, et al., eds. *Sexually Transmitted Diseases.* 3rd ed. New York: McGraw-Hill; 1999:335-346.
4. Richart R, Masood S, Syrjanen K, et al. Human papillomavirus IAC Task Force Summary. *Acta Cytol.* 1998;42:50-58.
5. Lorincz A, Reid R, Jenson A, Greenberg M, Lancaster W, Kurman R. Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. *Obstet Gynecol.* 1992;79:328-337.
6. World Health Organization. *IARC Monograph on the Evaluation of Carcinogenic Risks to Humans: Human Papillomaviruses.* Vol. 64; Lyons: IARC; 1995.
7. Schiffman M. Recent progress in defining the epidemiology of human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst.* 1992;84:394-398.
8. Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet.* 1974(i):1037-1040.
9. Kessler I. Venereal factors in human cervical cancer: evidence from marital clusters. *Cancer.* 1977;39:1912-1919.
10. Kiviat N, Koutsky L, Paavonen J. Cervical Neoplasia and Other STD-Related Genital Tract Neoplasias. In: Holmes K, Mardh P, Sparling P, et al., eds. *Sexually Transmitted Diseases.* 3rd ed. New York: McGraw-Hill; 1999:811-832.
11. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. *J Natl Cancer Inst.* 1995;87:796-802.
12. Walboomers J, Jacobs M, Manos M, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189:12-19.
13. Munoz N, Bosch F. The causal link between HPV and cervical cancer and its implications for prevention of cervical cancer. *Bull PAHO.* 1996;30(4):362-377.
14. Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med.* 1997;102 (5A):3-8.
15. Koutsky L, Holmes K, Critchlow M, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med.* 1992;327:1272-1278.
16. Ho G, Burk R, Klein S, et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst.* 1995;87:1365-1371.
17. Southern S, Herrington C. Molecular events in uterine cervical cancer. *Sex Transm Dis.* 1998;74:101-109.
18. National Institutes of Health. Cervical Cancer. *NIH Consensus Statement.* 1996;14(1):1-38.
19. Frisch M, Glimelius B, van den Brule J, Wohlfahrt J, Meijer C, Walboomers J. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med.* 1997;337:1350-1358.
20. Bjorge T, Dillner J, Anttila T, et al. A prospective seroepidemiological study of the role of human papillomavirus in non-cervical anogenital cancers. *Br Med J.* 1997;15:646-649.
21. Maden C, Sherman K, Beckmann A, Hislop T, Teh C, Daling J. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *J Natl Cancer Inst.* 1993;85:19-24.
22. Pisani P, Parkin D, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiol Biomarkers and Prev.* 1997;6:387-400.

23. Koutsky L, Kiviat NB. Genital Human Papillomaviruses. In: Holmes K, Mardh P, Sparling P, et al., eds. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999:347-360.
24. Svare EK, SK, Nonnemacher B, Worm A, et al. Seroactivity to human papillomavirus type 16 virus-like particles is lower in high-risk men than in high-risk women. *J Infect Dis*. 1997;176:876-883.
25. Wideroff L, Schiffman M, Hoover R, et al. Epidemiologic determinants of seroactivity to human papillomavirus (HPV) type 16 virus-like particles in cervical HPV-16 DNA-positive and -negative women. *J Infect Dis*. 1996;174:937-943.
26. Ho G, Bierman R, Beardsley L, Chang C, Burk R. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338:423-428.
27. Baken L, Koutsky L, Kuypers J, et al. Genital human papillomavirus infection among male and female sex partners: prevalence and type-specific concordance. *J Infect Dis*. 1995;171:429-432.
28. Svare E, Kjaer S, A W, et al. Risk factors for HPV infection in women from sexually transmitted disease clinics: comparison between two areas with different cervical cancer incidence. *Cancer*. 1998;75:1-8.
29. Strickler H, Kirk G, Figueroa J, et al. HPV 16 antibody prevalence in Jamaica and the United States reflects differences in cervical cancer rates. *Int J Cancer*. 1999;80:339-344.
30. Eddy D. Screening for cervical cancer. *Ann Intern Med*. 1990;113:214-226.
31. Kurman R, Henson D, Herbst A, Noller K, Schiffman M. Interim guidelines for management of abnormal cervical cytology. *JAMA*. 1994;271:1866-1869.
32. World Health Organization. The current status of development of prophylactic vaccines against human papillomavirus infection. 1999. Report No.: WHO/V&B/99.04.
33. Ries L, Kosery C, Hankey B, Miller B, Clegg L, Edwards B. SEER Cancer Statistics Review 1973-1996. Vol. NIH Pub. No. 99-2789. Bethesda, MD: National Cancer Institute; 1999.
34. Melbye M, Rabkin C, Frisch M, Biggar R. Changing patterns of anal cancer incidence in the United States, 1940-1989. *Am J Epidemiol*. 1994;139:772-780.
35. Goldie S, Kuntz K, Weinstein M, Freedberg K, Welton M, Palefsky J. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA*. 1999;281:1822-1829.
36. Chuang TY. Condyloma acuminatum in Rochester, Minnesota, 1950—1978. I. Epidemiology and clinical features. *Arch Dermatol*. 1984;120:469-475.
37. Armstrong L, Preston E, Reichert M. Incidence and prevalence of recurrent respiratory papillomatosis (RRP) among juveniles in the Atlanta and Seattle areas. . 15th International Papillomavirus Conference. Siena, Italy; 1997.
38. American Social Health Association. Sexually Transmitted Diseases in America: How Many Cases and at What Cost? 1998.
39. Siegal J. The economic burden of sexually transmitted diseases in the United States. In: Holmes K, Mardh P, Sparling P, et al., eds. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999:1367-1380.
40. Kotloff K, Wasserman S, Russ K, et al. Detection of genital human papillomavirus and associated cytological abnormalities among college women. *Sex Transm Dis*. 1998;25:243-250.
41. Munoz N, Kato I, Bosch F, et al. Risk factors for HPV DNA detection in middle-aged women. *Sex Transm Dis*. 1996;23:504-510.
42. Wheeler C, Parmenter C, Hunt W, et al. Determinants of genital human papillomavirus infection among cytologically normal women attending the University of New Mexico student health center. *Sex Transm Dis*. 1993;20:286-289.
43. Karlsson R, Jonsson M, Edlund K, et al. Lifetime number of partners as the only independent risk factor for human papillomavirus infection: a population-based study. *Sex Transm Dis*. 1995;22:119-126.

44. Kjellberg L, Wang Z, Wiklund F, et al. Sexual behavior and papillomavirus exposure in cervical intraepithelial neoplasia: a population-based case-control study. *J Gen Virol.* 1999;80:391-398.
45. Burk RD, Kelly P, Feldman J, et al. Declining prevalence of cervicovaginal human papillomavirus infection with age is independent of other risk factors. *Sex Transm Dis.* 1996;23:333-341.
46. Burk RD, Ho GYF, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. *J Infect Dis.* 1996;174:679-689.
47. Figueroa J, Ward E, Luthi T, Vermund S, Brathwaite A, Burk R. Prevalence of human papillomavirus among STD clinic attenders in Jamaica: association of younger age and increased sexual activity. *Sex Transm Dis.* 1995;22:114-118.
48. Hildesheim A, Gravitt P, Schiffman M, et al. Determinants of genital human papillomavirus infection in low-income women in Washington, D.C. *Sex Transm Dis.* 1993;20:279-285.
49. Fairley C, Chen S, Ugoni A, Tabrizi S, Forbes A, Garland S. Human papillomavirus infection and its relationship to recent and distant sexual partners. *Obstet Gynecol.* 1994;84:755-759.
50. Hippelainen M, Syrjanen S, Hippelainen M, et al. Prevalence and risk factors of genital human papillomavirus (HPV) infections in healthy males: a study on Finnish conscripts. *Sex Transm Dis.* 1993;20(321):328.
51. Roden R, Lowy D, Schiller J. Papillomavirus is resistant to desiccation. *J Infect Dis.* 1997;176:1076-9.
52. Rice P, Cason J, Best J, Banatvala J. High risk genital papillomavirus infections are spread vertically. *Rev Med Virol.* 1999;9:15-21.
53. Cubie H, Plumstead M, Zhang W, de Jesus O, Duncan L, Stanley M. Presence of antibodies to human papillomavirus virus-like particles (VLPs) in 11-13 year-old schoolgirls. *J Med Virol.* 1998;56:210-216.
54. af Geijersstam V, Eklund C, Wang Z, et al. A survey of seroprevalence of HPV types 16, 18, and 33 among children. *Int J Cancer.* 1999;80:489-493.
55. Ley C, Bauer H, Reingold A, et al. Determinants of genital human papillomavirus infection in young women. *J Natl Cancer Inst.* 1991;83:997-1003.
56. Fairley C, Chen S, Tabrizi S, et al. The absence of genital human papillomavirus infection in virginal women. *International Journal of STD and AIDS.* 1992;3:414-417.
57. Gutman L, St Claire K, Herman-Giddens M, Johnston W, Phelps W. Evaluation of sexually abused and nonabused young girls for intravaginal human papillomavirus infection. *Am J Dis Child.* 1992;146(6):694-699.
58. Kashima H, Shah F, Lyles A, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. *Laryngoscope.* 1992;102:9-13.
59. Bauer HM, Ting Y, Greer CE, et al. Genital human papillomavirus infection in female university students as determined by a PCR-based method. *JAMA.* 1991;265:472-477.
60. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. *Sex Transm Dis.* 1993;20:274-278.
61. Melkert PJ, Hopman E, van den Brule J, Risse E, Van Diest P, Bleker O. Prevalence of HPV in cytologically normal cervical smears, as determined by the polymerase chain reaction, is age-dependent. *Int J Cancer.* 1993;53:919-923.
62. Schneider A, Kirchoff T, Meinhardt G, Gissmann L. Repeated evaluation of human papillomavirus 16 status in cervical swabs of young women with a history of normal papanicolaou smears. *Obstet Gynecol.* 1992;79:683-688.
63. Moscicki A, Palefsky J, Smith G, Siboshski S, Schoolnik G. Variability of human papillomavirus DNA testing in a longitudinal cohort of young women. *Obstet Gynecol.* 1993;82:578-585.
64. Wheeler C, Greer C, Becker T, Hunt W, Anderson S, Manos M. Short-term fluctuations in the detection of cervical human papillomavirus DNA. *Obstet Gynecol.* 1996;88:261-268.

65. Nobbenhuis M, Walboomers J, Helmerhorst T, et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet*. 1999;354:20-25.
66. Hildesheim A, Schiffman M, Gravitt P, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis*. 1994;169:235-240.
67. Manos M, Kinney W, Hurley L, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal papanicolaou results. *JAMA*. 1999;281:1605.
68. Ronnett B, Manos M, Ransley J, et al. Atypical glandular cells of undetermined significance (AGUS): cytopathologic features, histopathologic results, and HPV DNA detection. *Hum Pathol*. 1999;30:816-25.
69. Kinney W, Manos M, Hurley L, Ransley J. Where's the high-grade cervical neoplasia? the importance of minimally abnormal Papanicolaou diagnoses. *Obstet Gynecol*. 1998;85:202-210.
70. Jenkins D, Sherlaw-Johnson C, Gallivan S. Assessing the role of HPV testing in cervical cancer screening. *Papillomavirus Rep*. 1998;9:89-101.
71. Cox J. Clinical role of HPV testing. *Obstet Gynecol Clinics NA*. 1996;23:811-851.
72. Cox J. Evaluating the role of HPV testing for women with equivocal papanicolaou test findings. *JAMA*. 1999;281:1645-1647.
73. Centers for Disease Control and Prevention. 1998 Guidelines for Treatment of Sexually Transmitted Diseases. *MMWR*. 1998;47(RR-1):1-116.
74. American College of Obstetrics and Gynecology. Cervical Cytology: Evaluation and management of abnormalities. *ACOG Technical Bulletin*. 1993(183):1-8.
75. Johnson K, The Canadian Task Force on the Periodic Health Examination. Periodic health examination, 1995 update: 1. Screening for human papillomavirus infection in asymptomatic women. *Can Med Assoc J*. 1995;152(4):483-493.
76. Kaufman R, Adam E. Does typing of human papillomavirus assist in the triage of women with repeated low-grade, cervical cytologic abnormalities? *Gynecol Oncol*. 1998;70:317-318.
77. Jenkins D, Sherlaw-Johnson C, Gallivan S. Can papilloma virus testing be used to improve cervical cancer screening? *Int J Cancer*. 1996;65:768-773.
78. Kaufman R, Adam E, Icenogle J, et al. Relevance of human papillomavirus screening in management of cervical intraepithelial neoplasia. *Am J Obstet Gynecol*. 1997;176:87-92.
79. Peyton C, Schiffman M, Lorincz A, et al. Comparison of PCR- and hybrid capture-based human papillomavirus detection systems using multiple cervical specimen collection strategies. *J Clin Microbiol*. 1998;36:3248-3254.
80. Ferris D, Wright Jr. T, Litaker M, et al. Comparison of two tests for detecting carcinogenic HPV in women with papanicolaou smear reports of ASCUS and LSIL. *J Fam Pract*. 1998;46:136-141.
81. Cox J. Management of cervical intraepithelial neoplasia. *Lancet*. 1999;353:857-859.
82. Chesebro M, Everett W, Lorincz A. High-risk human papillomavirus testing of women with cytological low-grade squamous intraepithelial lesions. *J Lower Genital Tract Dis*. 1997;1:234-239.
83. Wright Jr T, Lorincz A, Ferris D, et al. Reflex human papillomavirus deoxyribonucleic acid testing in women with abnormal papanicolaou smears. *Am J Obstet Gynecol*. 1998;178:962-966.
84. Sherman M, Schiffman M, Lorincz A, et al. Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer*. 1997;81:89-97.
85. Schiffman M, Adrianza E, Group. TAS. The ASCUS-LSIL Triage Study (ALTS): design, methods, and characteristics of trial participants. [manuscript in preparation]. .
86. Meijer C, van den Brule A, Snijders P, Helmerhorst T, Kenemans P, Walboomers J. Detection of human papillomavirus in cervical scrapes by the polymerase chain reaction in relation to cytology: possible implications for cervical cancer screening. In: Munoz N, Bosch F, Shah K, Meheus A, eds. *The*

- Epidemiology of Cervical Cancer and Human Papillomavirus*. Lyons: International Agency for Research on Cancer; 1992:271-281.
87. Dillner J. Can cervical cancer screening programs be improved by incorporating screening for human papillomavirus infection? *The Cancer Journal*. 1998;11:272-275.
 88. van Ballegooijen M, van den Akker-van Marie M, Warmerdam P, Meijer C, Walboomers J, Habbema J. Present evidence on the value of HPV testing for cervical cancer screening: a model-based exploration of the (cost-)effectiveness. *Br J Cancer*. 1997;76(5):651-657.
 89. Ponten J, Adami H, Bergstrom R, et al. Strategies for global control of cervical cancer. *Int J Cancer*. 1995;60:1-26.
 90. Cuzick J, Beverley E, Ho L, et al. The value of HPV testing in primary screening of older women. *Br J Cancer*. 1999;81:554-558.
 91. Schneider A, Zahm D, Kirchmayr R, Schneider V. Screening for cervical intraepithelial neoplasia grade 2/3: validity of cytologic study, cervicography, and human papillomavirus detection. *Am J Obstet Gynecol*. 1999;174:1534-1541.
 92. Ratnam S, Ghatage P, Franco E, Ferenczy A. Utility of HPV testing in combination with papanicolaou smear in primary cervical cancer screening. *17th International Papillomavirus Conference, Charleston, SC*. 1999.
 93. Hill R, Kuhn L, Denny L, Wright T, Sun X, Lorincz A. Use of HPV DNA testing for cervical cancer screening: results from the Khayelitsha study, South Africa. *17th International Papillomavirus Conference, Charleston, SC*. 1999.
 94. Clavel C, Masure M, Bory JP, et al. Hybrid Capture II-based human papillomavirus detection, a sensitive test to detect in routine high grade cervical lesions: a preliminary study on 1518 women. *Br J Cancer*. 1999;80:1306-11.
 95. Schiffman M, Herrero R, Hildesheim A, et al. HPV DNA testing for cervical cancer screening: results from 9,000 women in the NCI Guanacaste project. *JAMA*. 2000 (in press).
 96. Champion M, Cuzick J, McCance D, Singer A. Progressive potential of mild cervical atypia: prospective cytological, colposcopic, and virological study. *Lancet*. 1986;ii:237-240.
 97. Hording U, Junge J, Rygaard C, Lundvall F. Management of low-grade CIN: follow-up of treatment? *Eur J Obstet Gynecol Reprod Biol*. 1995;62:49-52.
 98. Liu T, Seng-jaw S, Alvarez R, Butterworth Jr. C. A longitudinal analysis of human papillomavirus 16 infection, nutritional status, and cervical dysplasia progression. *Cancer Epidemiology, Biomarkers, and Prevention*. 1995;4:373-380.
 99. Remmink A, Walboomers J, TJM H, et al. The presence of persistent high-risk HPV genotypes in dysplastic cervical lesions is associated with progressive disease: natural history up to 36 months. *Int J Cancer*. 1995;61:306-311.
 100. Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. *Obstet Gynecol*. 1986;67:665-669.
 101. Mitchell H, Medley G. Age and time trends in the prevalence of cervical intraepithelial neoplasia on Papanicolaou smear tests, 1970-1988. *Med J Aust*. 1990;152:252-255.
 102. Elfgrén K, Bistoletti P, Dillner L, Walboomers J, Meijer C, Dillner J. Conization for cervical intraepithelial neoplasia is followed by disappearance of human papillomavirus deoxyribonucleic acid and a decline in serum and cervical mucus antibodies against human papillomavirus antigens. *Am J Obstet Gynecol*. 1996;174:937-942.
 103. Mitchell M, Tortolero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstet Gynecol*. 1998;92(5):737-744.

104. Bollen L, Tjong-a-Hung S, van der Velden J, et al. Prediction of recurrent and residual dysplasia by human papillomavirus detection among patients with abnormal cytology. *Gynecol Oncol.* 1999;72:199-201.
105. American Cancer Society . *Guidelines for the cancer-related checkup: an update* Atlanta: American Cancer Society; 1993.
106. Hawkes A, Kronenberger C, MacKenzie T, et al. Cervical cancer screening: American College of Preventive Medicine practice policy statement. *Am J Prev Med.* 1996;12:342-344.
107. Woolf S. Screening for cervical cancer. In: DiGiuseppi C, Atkins D, Woolf S, eds. *Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force.* 2nd ed. Alexandria, Virginia: International Medical Publishing; 1996.
108. Crowther M. Is the nature of cervical carcinoma changing in young women? *Obstet Gynecol Surv.* 1994;50:71-82.
109. Mangan S, Legano L, Rosen C, et al. Increased prevalence of abnormal Papanicolaou smears in urban adolescents. *Arch Pediatr Adolesc Med.* 1997;151:481-484.
110. Cook GA, Draper GJ. Trends in cervical cancer and carcinoma in situ in Great Britain. *Br J Cancer.* 1984;3:367-375.
111. Bourne RG, Grove W. Invasive carcinoma of the cervix in Queensland. Change in incidence and mortality, 1959-1980. *Med J Aust.* 1983;138:156-158.
112. Walton R, Allen H, Anderson G, et al. Cervical cancer screening programs: Summary of the 1982 Canadian Task Force Report. *Can Med Assoc J.* 1983;127:581-589.
113. Devesa S, Young J, Brinton L, JFF. Recent trends in cervix uteri cancer. *Cancer.* 1989;64:2184-2190.
114. Silcocks B, Moss S. Rapidly progressive cervical cancer: is it a real problem? *Br J Obstet Gynaecol.* 1988;95:1111-1116.
115. Hildesheim A, Hadjimichael O, Schwartz P, et al. Risk factors for rapid-onset cervical cancer. *Am J Obstet Gynecol.* 1999;180:571-577.
116. Perlman S, Kahn J, Emans S. Should pelvic examinations and papanicolaou cervical screening be part of preventive health care for sexually active adolescent girls? *J Adol Health.* 1998;23:62-67.
117. Siegfried E, Rasnick-Conley J, Cook S, Leonardi C, Monteleone J. Human papillomavirus screening in pediatric victims of sexual abuse. *Pediatrics.* 1998;101:43-47.
118. Shafer M. Annual pelvic examination in the sexually active adolescent female: what are we doing and why are we doing it? *J Adol Health.* 1998;23:68-73.
119. Hillard P, Brown R. Adolescent pap smear screening: yes or no. *J Ped Adol Gynecol.* 1996;9:93-97.
120. Olamijulo J. Is cervical cytology screening of teenagers worthwhile? *Br J Obstet Gynaecol.* 1995;102:515-516.
121. O'Mahony C. There is no longer a place for underage cytology in genitourinary medicine clinics. *Genitourin Med.* 1996;70:433-434.
122. Van Oortmarsen G, Habbema J. Epidemiological evidence for age-dependent regression of pre-invasive cervical cancer. *Br J Cancer.* 1991;64:559-565.
123. Montz F. Impact of therapy for cervical intraepithelial neoplasia on fertility. *Am J Obstet Gynecol.* 1996;175:1129-1136.
124. Hillard P, Biro F, Wildey L. Complications of cervical cryotherapy in adolescents. *J Reprod Med.* 1991;36:711-716.
125. Brunham RC, Plummer FA. A general model of STD epidemiology and its implications for control. *Med Clin North Am.* 1990;74:1339-1352.
126. Garnett G, Anderson R. Sexually transmitted diseases and sexual behavior: insights from mathematical models. *J Infect Dis.* 1996;174(Suppl2):S150-S161.

127. Peters R, Thomas D, Hagan D, Mack T, Henderson B. Risk factors for invasive cervical cancer among Latinas and Non-Latinas in Los Angeles County. *J Natl Cancer Inst.* 1986;77:1063-1077.
128. Slattery M, Overall Jr J, Abbott T, French T, Robison L, Gardner J. Sexual activity, contraception, genital infections, and cervical cancer: support for a sexually transmitted disease hypothesis. *Am J Epidemiol.* 1989;130:248-258.
129. Grimes D, Economy K. Primary prevention of gynecologic cancers. *Am J Obstet Gynecol.* 1995;172:227-235.
130. Shlay J, McGill W, Masloboeva H, Douglas Jr J. Pap smear screening in an urban STD clinic: yield of screening and predictors of abnormalities. *Sex Transm Dis.* 1998;25:468-475.
131. Celentano DD, Klassen AC, Weisman CS, Rosenshein NB. The role of contraceptive use in cervical cancer: the Maryland cervical cancer case-control study. *Am J Epidemiol.* 1987;126:592-604.
132. Hildesheim A, Brinton L, Mallin K, et al. Barrier and spermicidal contraceptive methods and risk of invasive cervical cancer. *Epidemiol.* 1990;1:266-272.
133. Daling J, Weiss N. Are barrier methods protective against cervical cancer? *Epidemiol.* 1990;1:261-262.
134. Rosenthal S, Cohen S, Stanberry L. Topical microbicides: current status and research considerations for adolescent girls. *Sex Transm Dis.* 1998;25:368-377.
135. Hermonat P, Daniel R, Shah K. The spermicide nonoxynol-9 does not inactivate papillomavirus. *Sex Transm Dis.* 1992;19:203-205.
136. Sokal D, Hermonat P. Inactivation of papillomavirus by low concentrations of povidone-iodine. *Sex Transm Dis.* 1995;22:22-24.
137. Howett M, Neely E, Christensen N, et al. A broad-spectrum microbicide with virucidal activity against sexually transmitted viruses. *Antimicrob Agents Chemother.* 1999:314-321.
138. Beutner KR, Richwald GA, Wiley DJ, Reitano MV, AMA Expert Panel on External Genital Warts. External genital warts: report of the American Medical Association Consensus Conference. *Clin Infect Dis.* 1998;27:796-806.
139. Tyring S, Arany I, Stanley M, et al. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. *J Infect Dis.* 1998;178:551-555.
140. Ferenczy A, Mitao M, Nagai N, Silverstein S, Crum C. Latent papillomavirus and recurring genital warts. *N Engl J Med.* 1985;313:784-788.
141. Colgan TJ, Percy ME, Suri M, Shier RM, Andrews DF, Lickrish GM. Human papillomavirus infection of morphologically normal cervical epithelium adjacent to squamous dysplasia and invasive carcinoma. *Hum Pathol.* 1989;20:316-319.
142. Beutner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med.* 1997;102 (5A):28-37.
143. Krebs H, Helmkamp F. Treatment failure of genital condylomata acuminata in women: role of the male sexual partner. *Am J Obstet Gynecol.* 1991;165:337-340.
144. Kamb M, Fishbein M, Douglas J. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases. *JAMA.* 1998;280:1161-1167.
145. Laumann E, Gagnon J, Michael R, Michaels S. The number of partners. *The Social Organization of Sexuality.* Chicago: The University of Chicago Press; 1994:172-224.
146. Schiller J, Okun M. Papillomavirus vaccines: current status and future prospects. *Adv Derm.* 1996;11:355-381.
147. Galloway D. Is vaccination against human papillomavirus a possibility? *Lancet.* 1998;351(suppl III):22-24.
148. Hines J, Ghim S, Jenson A. Prospects for human papillomavirus vaccine development: emerging HPV vaccines. *Curr Opin Infect Dis.* 1998;11:57-61.

149. Anderson RM, Garnett GP. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet*. 1996;348:1010-1013.
150. Linnehan M, Andrews S, Groce N. College health providers' knowledge, attitudes, and management practices of genital HPV infection. *Nurse Pract*. 1996;21:122-129.
151. McClean H, Hillman R. Anogenital warts and condom use—a survey of information giving. *Genitourin Med*. 1997;73:203-206.
152. Reitano M. Counseling patients with genital warts. *Am J Med*. 1997;102(5A):38-43.
153. Clarke P, Ebel C, Catotti DN, Stewart S. The psychosocial impact of human papillomavirus infection: implications for health care providers. *Internat J STD AIDS*. 1996;7:197-200.
154. Institute of Medicine. *The Hidden Epidemic: Confronting Sexually Transmitted Diseases*. Washington, D.C.: National Academy Press; 1997. Eng T, Butler W, eds.
155. Champion MJ, Brown JR, McCance DJ, et al. Psychosexual trauma of an abnormal cervical smear. *Br J Obstet Gynaecol*. 1988;95:175-181.
156. Persson G, Dahlof L, Krantz I. Physical and psychological effects of anogenital warts on female patients. *Sex Transm Dis*. 1993;20:10-13.
157. Bell S, Porter M, Kitchener H, Fraser C, Fisher P, Mann E. Psychological response to cervical screening. *Prev Med*. 1995;24:610-616.
158. Goldman S, Glimelius B, Nilsson B, Pahlman L. Incidence of anal epidermoid carcinoma in Sweden, 1970-1984. *Acta Chir Scand*. 1989;155:191-197.
159. Daling J, Weiss N, Klopfenstein L, Cochran L, Chow W, Daifuku R. Correlates of homosexual behavior and the incidence of anal cancer. *JAMA*. 1982;247:1988-1990.
160. Daling J, Weiss N, Hislop T, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med*. 1987;317:973-977.
161. Holly E, Whittemore A, Aston D, Ahn D, Nickoloff B, Kristiansen J. Anal cancer incidence: genital warts, anal fissure or fistula, hemorrhoids, and smoking. *J Natl Cancer Inst*. 1989;81:1726-1731.
162. Koblin B, Hessol N, Zauber A, et al. Increased incidence of cancer among homosexual men, New York City and San Francisco, 1978-1990. *Am J Epidemiol*. 1996;144:916-923.
163. Palefsky J. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. *AIDS*. 1994;8:283-295.
164. Rabkin C, Biggar R, Melbye M, Curtis R. Second primary cancers following anal and cervical carcinoma: evidence of shared etiologic factors. *Am J Epidemiol*. 1992;136:54-8.
165. Palefsky J, Holly E, Gonzales J, Lamborn K, Hollander H. Natural history of anal cytologic abnormalities and papillomavirus infection among homosexual men with group IV HIV disease. *J Acquir Immune Defic Syndr Hum Retroviro*. 1992;5:1258-1265.
166. Critchlow C, Surawicz C, Holmes K, et al. Prospective study of high grade anal squamous intraepithelial neoplasia in a cohort of homosexual men: influence of HIV infection, immunosuppression and human papillomavirus infection. *AIDS*. 1995;9:1255-1262.
167. Goedert J, Cote T, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. *Lancet*. 1998;351:1833-1839.
168. Palefsky J, Holly E, Ralston M, Jay N, Berry M, Darragh T. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS*. 1998;12:495-503.
169. Melbye M, Cote T, Kessler L, Gail M, Biggar R, AIDS/Cancer Working Group. High incidence of anal cancer among AIDS patients. *Lancet*. 1994;343:636-639.
170. Vernon S, Holmes K, Reeves W. Human papillomavirus infection and associated disease in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21 (suppl 1):S121-S124.

171. Centers for Disease Control. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR*. 1999;48(RR-10):1-87.
172. de Ruiter A, Carter P, Katz D, et al. A comparison between cytology and histology to detect anal intraepithelial neoplasia. *Genitourin Med*. 1994;70:22-25.
173. Palefsky J, Holly E, Hogeboom C, Berry J, Jay N, et al. Anal cytology as a screening tool for anal squamous intraepithelial lesions. *Lancet*. 1997;351:1833-1839.
174. Goldie S, Kuntz K, Weinstein M, Freedberg K, Palefsky J. Cost-effectiveness of screening for anal squamous cell cancer in homosexual and bisexual men. *Am J Med*. 2000 (in press).
175. Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine M. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS*. 1998;12:1459-1464.
176. Centers for Disease Control, Division of STD Prevention. Sexually Transmitted Diseases Surveillance 1997. 1998.
177. Fleming D, McQuillan G, Johnson R, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med*. 1997;337(16):1105-1111.

