Cervical Cancer Prevention

Cervical cancer is an important women's reproductive health problem, especially in developing countries where an estimated 190,000 women die from the disease each year.

Unlike many cancers, cervical cancer can be prevented. This section of RHO provides information on cervical cancer, with a focus on women in developing countries and prevention of cancer through identification and treatment of precancerous lesions, not on treatment of invasive disease.

The Alliance for Cervical Cancer Prevention was launched in 1999 by EngenderHealth (formerly AVSC International), IARC (International Agency for Research on Cancer), JHPIEGO Corporation, PAHO (Pan American Health Organization), and PATH (Program for Appropriate Technology in Health). The five-year project, supported by the Bill & Melinda Gates Foundation, will support programs to clarify, promote, and implement strategies for preventing cervical cancer in developing countries.

RHO's Cervical Cancer Prevention section is funded by the Bill & Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention.

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
- Spanish Edition

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Overview/Lessons Learned

Introduction

Cervical cancer is an important women's health problem, especially in developing countries, where an estimated 190,000 women die from the disease each year (Pisani et al. 1999). It is the third most common cancer worldwide and the leading cause of death from cancer among women in developing countries. At least 466,000 new cases are identified each year; roughly 80 percent are in developing countries. Rates are highest in Central America, sub-Saharan Africa, and Melanesia (Path/*Outlook* 2000).

Unlike many cancers, cervical cancer is preventable. It can be prevented by using relatively inexpensive screening and treatment technologies to detect abnormal cervical tissue before it progresses to invasive cancer.

An important reason for the sharply higher cervical cancer incidence in developing countries is the lack of effective screening programs aimed at detecting precancerous conditions (dysplasia) and treating them before they progress. It has been estimated that only about 5 percent of women in developing countries have been screened for cervical dysplasia in the past 5 years, compared with some 40 to 50 percent of women in developed countries.

The vast majority of cases are caused by human papillomavirus (HPV), a sexually transmitted agent that infects the cells of the cervix and slowly causes cellular changes (dysplasia) that can result in cancer. These changes can be relatively mild ones that often do not progress and may even regress. Larger, deeper lesions (severe dysplasia) are more likely to progress to cancer (Nasiell et al. 1986; Holowaty et al. 1999). Women generally are infected with HPV in their teens, 20s, or 30s; the disease can take up to 20 years after HPV infection to develop. Cervical cancer starts with an in situ stage that can be treated, but then progresses to invasive disease that is always fatal where surgery and radiation therapy are

unavailable.

Top of page

The traditional approach to prevention

Cervical cancer prevention efforts worldwide have focused on screening women at risk of the disease using Pap smears and treating precancerous lesions. Where screening quality and coverage have been high, these efforts have reduced invasive cervical cancer by as much as 90 percent (Gustafsson et al. 1997).

Most developing counties, however, have been unable to implement comprehensive, Pap smear screening–based programs. In countries where Pap smear screening is available, it often is accessible only to a small proportion of women through private-sector health care providers, or it is offered primarily to young women through maternal and child health or family planning clinics where the population being screened generally is not at high risk (Robles et al. 1996). These approaches have had little effect on morbidity and mortality, and generally are not as cost-effective as centrally organized screening programs implemented by the public sector (Fahs et al. 1996). A cost-effectiveness study of Pap screening services in Vietnam suggested that costs for establishing *de novo* pap screening may be reasonable in some settings with additional support from international funders (Suba et al. 2001).

Top of page

Emerging strategies

Some countries have redesigned their cervical cancer screening programs to be more successful and effective. Strategies have been developed to limit screening to women at highest risk of high-grade dysplasia, to reduce the frequency of screening among women who have had at least one normal smear, and to recommend regular follow-up rather than treatment for young women with mildly abnormal smears. Even screening women in their 30s once in a lifetime can have a significant effect on mortality (Murthy et al. 1993; Goldie et al. 2001; Mandelblatt et al. 2002). Modified screening and treatment strategies, an increased emphasis on improving the accuracy of the tests, planning for follow-up of clients, and evaluation of the program are key to program success. A 1998 workshop in Kenya on the prevention and control of cervical cancer in East and southern Africa discussed these issues and developed local plans of action. [View a PDF of the meeting report. PDF file requires Adobe Acrobat Reader.]

Several alternative approaches to cervical cancer screening also have been proposed and are being evaluated in research studies. These include visual screening (both magnified and unmagnified visual screening) to identify cervical lesions without reliance on cytology; HPV tests that may be able to identify women at high risk for cervical cancer, and automated Pap screening machines to identify subsets of Pap smears that should be examined by cytologists. These approaches are being evaluated for clinical effectiveness, acceptability to clients and health care providers, and cost-effectiveness (see the Screening: assessment of alternative approaches key issue for more information).

In 1997 representatives of three international nongovernmental organizations working to prevent cervical cancer in developing countries met with representatives of USAID and identified ten research questions felt to be of highest priority in guiding strategy development for preventing cervical cancer in low-resource settings (Sherris 1999).

In 1999, with support from the Bill & Melinda Gates Foundation, the Alliance for Cervical Cancer Prevention was formed to take the critical next steps in clarifying, promoting, and implementing effective prevention strategies, in partnership with developing-country counterparts.

Top of page

Lessons learned

In order to reduce cervical cancer morbidity and mortality, experience shows that, at a minimum, programs with limited resources should strive to:

- Increase awareness of cervical cancer and preventive health-seeking behavior among high-risk women (30 to 50 is a reasonable target age-group for new cervical cancer control programs with limited resources).
- Screen all women aged 30 to 50 at least once before expanding services to other age groups or decreasing the interval between screening.
- Treat women with high-grade dysplasia, refer those with invasive disease where possible, and provide palliative care for women with advanced cancer.
- Collect service delivery statistics that will facilitate ongoing monitoring and evaluation of program activities and outputs.

Other lessons learned include:

- Strong management and support for program strategies at all levels of the health care system are essential.
- Crucial to gaining this support is clearly demonstrating the need and demand for a cervical cancer control program.
- Demonstrating this need should include analyses of the estimated costs and impact of various program approaches.
- Health care providers and clients should be involved in program design to ensure that their perspectives are considered and their needs are met.
- Potential bottlenecks to program functioning (for example, logistical barriers) should be identified and addressed at the start.
- Effective programs rely on health care providers trained to be sensitive to client concerns and needs.

Go to Key Issues Top of Page

Cervical Cancer Prevention

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Cervical Cancer Consultative Group:
Ten Priority Questions Regarding Cervical Cancer Prevention in Developing Countries

The following questions were developed by representatives of AVSC International, the JHPIEGO Corporation, PATH (Program for Appropriate Technology in Health) and the U.S. Agency for International Development, who met in 1997 to evaluate research and programming needs. The group evaluated a list of 30 questions that could be answered through medical or operations research, policy or cost analysis, or development of programming or research guidelines. From among these questions, 10 were identified as high priority. These questions were selected based on the following criteria: they can be answered in 2 to 3 years; they are not being fully addressed; they can be answered, in part, by supplementing ongoing projects and activities in specific countries; their answers can facilitate the design of effective programs in low-resource settings; and their answers will respond to the concerns of donors, aid agencies, women's health advocates, and program managers and planners.

1. What are the sensitivity and specificity of visual inspection (aided and unaided)? How can specificity be maximized?

2. What are the common side effects of LEEP and cryotherapy?

3. What characteristics define the target group for which screening has the most impact?

4. When should low-grade dysplasia be treated?

5. How effective are the requirements for integrating cervical cancer prevention interventions into existing health and family planning services?

6. How do we ensure that policy makers implement effective program strategies? How are cervical cancer resources expended now?

7. What are the perspectives of clients, providers, program managers, women's health advocates, and others regarding cervical cancer control? What are the implications of these perspectives for the design of appropriate control programs?

8. How do various screening approaches perform in routine settings in terms of sensitivity and specificity, coverage and cost-effectiveness?

9. What are women's experiences with LEEP and cryotherapy?

10. What level of support is needed to maintain high-quality cervical cancer prevention services (such as in equipment and provider skills, among others)?

Back to Overview & Lessons Learned Top of page

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
- Spanish Edition

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Key Issues

This section provides brief summaries of some of the major research areas related to cervical cancer control in low-resource settings. More detailed discussions of specific key issues are included in the Annotated Bibliography.

- Epidemiology and natural history of cervical cancer
- Primary prevention of cervical cancer
- Screening: assessment of alternative approaches
- Treatment: evaluation of simple approaches
- Role of HPV tests in cervical cancer prevention
- The promise of HPV vaccines
- Cervical cancer and HIV
- Client perceptions

Be sure to use the Glossary if you are unfamiliar with any of the terms on this page.

Epidemiology and natural history of cervical cancer

Cervical cancer develops slowly, and the key precursor is severe dysplasia. Mild dysplasia almost always regresses spontaneously; most moderate dysplasias also regress (Holowaty et al. 1999; Critchlow and Kiviat 1999). Human papillomavirus (HPV) probably is the cause of almost all cervical cancer worldwide (Bosch et al. 1995; Schiffman 1995; Pisani et al. 1997; Hernandez-Avila et al. 1997). A recent study estimates worldwide HPV prevalence in cervical carcinomas at 99.7 percent (Walboomers et al. 1999). Even so, results from the longest longitudinal study of incident HPV infections suggest that, within 36 months of HPV infection, 90 percent of young women had cleared the infection (Moscicki et al. 2001). The risk for developing high-grade cervical lesions appears to be associated, in general, with the persistence of HPV infection and, in particular, with type-specific persistence (Kjaer et al. 2002). Studies also suggest that persistence of HPV infection is related to the development of cancer (Moscicki et al. 2001; Wallin et al. 1999; Burk 1999). Besides HPV, other risk factors appear to include certain sexual activity patterns and smoking (Brinton 1992;

Biswas et al. 1997; Prokopczyk et al. 1997, Roteli-Martins et al. 1998; Wen et al. 1999; Kjellberg et al. 2000; Moscicki et al. 2001). Recent evidence from IARC's multi-center, case-control studies suggests that both oral contraceptive use and high parity have a significant association with increased risk for cervical cancer (Muñoz et al. 2002; Moreno et al. 2002). Interpretations of the data are complex, and multiple confounding factors may be playing a role. Certain sexually transmitted infections (STIs) such as *Chlamydia trachomatis* and herpes simplex virus also may be associated with an increased risk of developing cervical cancer (Anttila et al. 2001; Zenilman 2001; Moscicki et al. 2001; Smith et al. 2002).

In some developing countries, there is concern among clinicians that cervical cancer develops differently from what is traditionally described in Western countries (for example, concern that cervical cancer may develop at younger ages and that dysplasia progresses more quickly to invasive disease) (Rogo et al. 1990). A study of Pap smear results from ob/gyn clinics in South Africa found that a significant proportion of cervical cancer cases occurred in women younger than age 40 (Lancaster et al. 1999). Whether these results would have been the same with a true population-based sample is unclear. In fact, data from a population-based study in Ontario, Canada, showed a pattern of HPV prevalence consistent with a population-based study conducted in Costa Rica. In both studies, prevalence of carcinogenic HPV peaked among women under the age of 25 and had a second peak in women 59 years of age and older (Sellors et al. 2002). Population-based data from two provinces in Thailand show a similar pattern of high-risk HPV infection in younger women, with the prevalence of high-risk HPV peaking in women under the age of 25 and between the ages of 25 and 34 (Sukvirach et al. 2003). Overall, few studies have conclusively demonstrated regional differences in the age-specific risk of cervical cancer; in general, cervical cancer risk peaks about age 50, and severe dysplasia risk peaks about age 35 (Ponten et al. 1995).

Top of Page

Primary prevention of cervical cancer

Although primary prevention of HPV infection would greatly reduce cervical cancer mortality, the prevention of HPV transmission presents greater challenges than most STIs. HPV generally is asymptomatic and easily transmitted. The virus can exist throughout most of the anogenital area (including areas not covered by male condoms). Although treatment strategies are available for the genital warts sometimes caused by HPV, no therapies exist to eliminate the underlying infection (Koutsky et al. 1999; PATH/*Outlook* 1998). It is not entirely clear that barrier methods of protection against STIs are effective in protecting women from cervical cancer. A number of studies have found barrier methods to be protective (Grimes et al. 1995; Coker et al. 1992; Thomas et al. 1996), including one study that found condom use significantly reduced the risk of acquiring genital warts (Wen et al. 1999). Other studies have not found a significant association between use of barrier methods and cervical cancer prevention (Hildesheim et al. 1990). HPV DNA also has been detected on the fingertips of persons with genital warts, suggesting a potential for transmission of HPV infection by finger-genital contact (Sonnex et al. 1999), although this may be an unlikely route of transmission (Mindel and Tideman 1999). Researchers also are beginning to focus on the possible role of men who may be acquiring high-risk HPV from frequent contact with sex workers and transmitting the infection to their wives (Thomas et al. 2001). Results from pooled data from IARC's seven case-control studies shows a strong association between circumcision and a reduced risk of penile HPV and subsequent cervical cancer in female partners (Castellsague et al. 2002). Interpretation of the data is complex because of possible confounding factors and the reliability of self-reported circumcision status. Certainly, sexual abstinence or lifetime mutually monogamous relationships would prevent the transmission of HPV; however, these options may not be realistic for many individuals. Other suggestions of primary prevention strategies for cervical cancer are based on risk associations in case-control studies and include avoidance of cigarette smoking and maintaining a high dietary intake of vitamin C (Grimes et al. 1995). Both the World Health Organization (WHO) and the National Institutes of Health (NIH) also recommend sexuality education and efforts to change sexual behavior as part of their primary prevention strategies (WHO 1985; NIH Consensus Statement 1986; Shepherd et al. 1999).

Top of Page

Screening: assessment of alternative screening approaches

In industrialized countries, cervical cancer incidence and mortality have been reduced significantly through Pap smear screening and biopsy, followed by treatment of cervical dysplasia. The effectiveness of this approach is dependent on a relatively high level of infrastructure that is not easily established or maintained in the developing world. A study in five African countries revealed that even where the basic infrastructure was in place, very few women were being screened (Chirenje et al. 2001). Even in Latin America, where Pap smear screening programs have been in place for some time, results to date have not shown a significant impact on cervical cancer prevention (Robles 1996; Lazcano-Ponce et al. 1999; Hernandez-Avila 1998). Often, Pap-smear screening programs have not adequately served older women, who have the highest risk of cervical cancer. Pap smear quality and coverage often are low. In addition, even in middle-income countries, program organization to adequately manage, treat, and follow-up women with identified lesions can be a challenge (Sankaranarayanan et al. 2001). Also, Pap tests themselves have shortcomings: high specificity in Pap smear testing cannot be achieved without reducing sensitivity. The WHO *Reproductive Health Library* includes a summary of a meta-analysis of Pap test accuracy that reviewed 62 studies and concluded "the Pap test may be unable to achieve concurrently high sensitivity and specificity" (Fahey 1995). To address these limitations, a number of new cervical cancer screening approaches are being evaluated, including visual inspection, automated Pap screening, alternative approaches to specimen collection, and protocols using HPV tests (Richart 1995; Spitzer 1998; Manos et al. 1999; Pengsaa et al. 1997; Hillemanns et al. 1999; Sellors et al. 2000; Meijer et al. 2000).

For low-resource settings, there is particular interest in the accuracy and acceptability of visual screening as a means of detecting cervical dysplasia or cancer (Megevand 1996; PATH/*Outlook* 2000). This type of screening may reduce the cost and complexity of Pap smear screening, and holds the potential for screening and treatment in the same visit. The term "visual inspection" (VI) has been used to refer to methods of examining the cervix for obvious lesions (Nene et al. 1996; Wesley et al. 1997). A study in India comparing unaided VI (also known as "downstaging") and Pap smear results showed that VI had low sensitivity and specificity in detecting cervical dysplasias (Varghese 2000). A second study that assessed downstaging to detect high-grade cervical lesions concluded that neither a low-threshold nor a high-threshold test was adequate for primary screening of cervical lesions (Basu et al. 2002).

A more promising visual screening approach, visual inspection with acetic acid (VIA), is used to describe examination of the cervix after treatment with acetic acid to identify acetowhite lesions. In some settings, visual inspection after acetic acid application may work at least as well as Pap smears. A qualitative summary of the literature reports that in those settings where VIA has been compared to cytology under similar circumstances, VIA has performed as well as, if not better than, cytology in some instances (Gaffikin et al. 2003). Analyses from a growing number of studies in developing-country settings indicate the sensitivity of VIA is equivalent or greater than cytology, although its specificity is somewhat lower (Sankaranarayanan et al. 2004a; Sankaranarayanan et al. 2004b; Basu et al. 2003; Sankaranarayanan et al. 2003; Belinson et al. 2001; Sankaranarayanan et al. 1999; UZ/JHPIEGO 1999; Sankaranarayanan et al. 1998.) Several studies have also evaluated VIA as an adjunctive test for screening in order to increase its specificity. A two-stage screening study in South Africa recommends that VIA be followed by a second, different screening test if the VIA is positive (Denny et al. 2000). An analysis of the data from the Zimbabwe study shows that following VIA with a second screening test, such as an HPV DNA test, improves overall specificity, thus reducing the number of false-positives (Blumenthal et al. 2001).

To complement the growing body of evidence of the accuracy of VIA, a recent study examined the reliability of VIA. The data show moderate to substantial inter-rater reliability for clinicians' assessment of cervical photographs taken after using the acetic acid wash. This reliability statistic is comparable to similar tests of inter-rater agreement for coloposcopy, cervical cytology, and histology (Sellors et al. 2002), and is a significant step toward validating the accuracy of the test.

Other forms of visual inspection, such as visual inspection with acetic acid and low-power magnification (VIAM) and visual inspection with Lugol's iodine (VILI) also are being investigated. VIAM using the AviScope™ device yielded a moderate sensitivity of 60.0 percent for identifying CIN 2, CIN 3, or carcinoma, and a moderate specificity of 69.0 percent in a recent study (Winkler et al. 2003). A second study reported a similar sensitivity of 61 percent and a specificity of 83 percent (Basu et al. 2003). While these results are promising for areas where colposcopy is not available, the clinical utility of the device is still being explored. VILI, which is similar to the Schiller's iodine test used in the 1930's has been reevaluated in a recent study as an alternative for use in low-resource settings. Results indicate that VILI has a similar sensitivity and specificity to that of VIA (using a high-threshold cut-off), suggesting it is a promising and suitable alternative to cytology in low-resource settings (Sankaranarayanan et al. 2003). The largest set of pooled data on VILI indicates that it is more sensitive than VIA and at least as specific (Sankaranarayanan 2004b).

Researchers have also been developing mathematical models to evaluate the cost-benefits of alternative screening strategies such as VIA. In a model based on data from Thailand, VIA saved the greatest number of lives and was associated with the least costs, when used to screen women between the ages of 35–55 at five-year intervals and coupled with immediate treatment of positive results (Mandelblatt et al. 2002). A second model based on data from South Africa determined that visual inspection with acetic acid followed by immediate treatment resulted in a 26 percent reduction in cervical cancer incidence and was a cost-savings (Goldie et al. 2001). In addition, a model comparing opportunistic screening to organized screening indicated that greater effectiveness (as determined by the percent reduction in cervical cancer incidence) can be achieved most efficiently if screening is conducted in an organized program and can achieve 80 percent coverage of the population (Adab et al. 2004).

Despite the promising controlled research studies on visual inspection, its application in mass screening programs needs to be carefully considered. Given the potential for overtreatment in a "see and treat" protocol, the complications of treatment in low-resource settings need to be evaluated (Cullins et al. 2000). A recent study in Thailand provides reassurance about the safety of immediate treatment with cryotherapy. When performed by trained nurses, cryotherapy was associated with no major complications and with minimal, unexpected problem visits for minor complications (Gaffikin et al. 2003). (For more information, please see the Treatment Key Issue.) An additional issue that needs to be addressed is the interaction between increasing age and the effectiveness of visual inspection (Zahm et al. 1998).

Other visual screening approaches include cervicography and speculoscopy, but they appear to be less promising for various technical and programmatic reasons (Spitzer 1998; Schneider 1999). A device called a Polarprobe, which evaluates a woman's cervical health by processing electrical and optical properties of cervical tissue, may hold promise (Coppleson et al. 1994; Spitzer 1998).

Top of Page

Treatment: evaluation of simple approaches

Two outpatient dysplasia treatment approaches have demonstrated particular utility in low-resource settings (Bishop et al. 1995). These are cryotherapy (freezing of diseased tissue through application of a refrigerated probe) and the loop electrosurgical excision procedure (LEEP), which uses a thin electrified wire to excise cervical lesions. These methods have been found to have comparable rates of successes and complications (Mitchell et al. 1998). Cryotherapy is a simple, inexpensive procedure and does not require electricity. Twelve months after treatment, cryotherapy has been associated with cure rates of approximately 80 to 90 percent (ACCP 2003; Andersen and Husth 1992; Olatunbosun et al. 1992). Cryotherapy generally produces a lower cure rate for larger lesions and for lesions that extend into the cervical canal. Complications associated with cryotherapy are minimal, suggesting that offering cryotherapy in settings where women may not have access to follow-up medical care may be a rational approach (ACCP 2003). In addition, cost-effectiveness modeling has shown that cryotherapy is a cost-effective approach compared to other methods such as LEEP, laser

ablation, cold knife conization, and total hysterectomy, while still providing an effective treatment (Kleinberg et al. 2003). LEEP, on the other hand, has been associated with cure rates of about 80 to 93 percent (Flannelly et al. 1997; Hulman et al. 1998; Keijser et al. 1992), and may be the preferred method for treating larger, deeper lesions. Compared to cryotherapy, LEEP has been associated with slightly higher rates of complications and side effects such as postoperative bleeding and perioperative pain (Mitchell et al. 1998). The likelihood of cure for both methods decreases with higher-grade lesions and larger lesions. Older age also may be associated with lower cure rates (Mitchell et al. 1998; Paraskevaidis et al. 2000) possibly because older women are more likely to have persistent, higher-grade lesions.

An area of current research interest is whether these treatment approaches can be used in a "see and treat" strategy, in which a client is diagnosed with dysplasia either through a Pap smear, visual screening, or colposcopic exam, and then is treated immediately to remove dysplastic tissue. This approach has been tried in various research settings, including in the United States (Burger et al. 1995) and South Africa, using mobile clinics (Megevand et al. 1996). The approach shows promise because it allows management and treatment decisions to be made in a single visit, reducing the loss to follow-up of many women who may be at high risk (Blumenthal et al. 2001). An evaluation of the single-visit approach using VIA and cryotherapy treatment in Thailand found the approach to be safe, acceptable, and feasible (Gaffikin et al. 2003), with no reported major complication associated with cryotherapy . Unnecessary treatment, however, remains a concern in some settings. Despite the progress in treatment approaches, a global survey found that clinicians in developing countries still rely heavily on invasive inpatient methods, such as cone biopsy and hysterectomy, and in many places all degrees of cervical dysplasia were treated (Bishop et al. 1996).

Top of Page

Role of HPV tests in cervical cancer prevention

Research is ongoing to determine acceptable protocols for testing for the human papillomavirus (HPV) as part of a cervical screening and treatment strategies. Proposed uses of HPV testing in cervical cancer prevention programs include:

1. Where Pap smear screening is the norm, as a triage for women with Pap smear findings of atypical squamous cells of unknown significance, that is, cells that are atypical but not definitely dysplasia (women who test positive for high-risk HPV types would be monitored closely or referred for colposcopy).
2. As a means of surveillance of women after treatment for high-grade lesions or microinvasive cancer (those who test positive for high-risk HPV types would be monitored more closely than those who test negative).
3. Among women aged 30 to 35 or older (those who test positive for high-risk HPV would undergo diagnosis via colposcopy or another visualization technique) (Cuzick 2000).

In general, however, proposed approaches such as administering HPV tests to women with mild dysplasia in order to determine whether treatment is necessary have had varying levels of effectiveness and are likely to be relatively costly (Bollen et al. 1997; Kaufman et al. 1997; Lytwyn 2000).

Persistent HPV infection appears to be a clear risk factor for persistent cervical intraepithelial neoplasia (CIN II) (Ho et al. 1995), and type-specific persistence of high-risk HPV infection is a good predictor of developing high-grade lesions (Kjaer et al. 2002). HPV appears to be a stronger predictor of persistent cervical abnormalities in women over age 35 (Spitzer 1998). Certain types of HPV and persistent high loads of viral infection may be associated with increased risks of cervical neoplasia (Ylitalo et al. 2000; Joseffson et al. 2000), but whether this justifies HPV DNA screening is still open to debate (Johnston 2000; Elfgren et al. 2000). HPV remains detectable longer than cervical cytologic abnormalities, suggesting that HPV DNA testing may be a more sensitive test for HPV infection and that there may be a role for HPV-DNA testing in women with ambiguous cytology results (Schiffman et al. 2002).

Recently, work has been published evaluating use of HPV DNA testing for primary screening for cervical cancer, particularly in low-resource settings. A study in Costa Rica, for example, assessed test cut-off points and the importance of women's age on test effectiveness at detecting high-grade cervical lesions or cancer (Schiffman et al. 2000). Research on HPV testing has included assessments of the accuracy and acceptability of different sampling methods with the expectation that self-sampling methods could help increase participation in cervical cancer screening. A study in South Africa found that HPV DNA testing using self-collected vaginal samples performed quite well compared to conventional Pap screening in that setting (Wright et al. 2000; Denny et al. 2000). Women participating in a study in Mexico overall rated self-collected samples for HPV as more acceptable than traditional Pap smear screening (Dzuba et al. 2002). A study in Zimbabwe evaluated HPV-based screening in a population at high risk for HIV infection (Womack 2000). Specificity remains a concern with use of HPV testing for primary screening, however, and more research is needed to determine optimal approaches (Cuzick 2000; Koss 2000). One study in South Africa suggests that specificity can be improved by adjusting the level of HPV DNA used to define a positive result (Kuhn et al. 2000).

Top of Page

The promise of HPV vaccines

Prospects are hopeful for the utility of HPV vaccines. Products currently in development include prophylactic vaccines (which would prevent HPV transmission) and therapeutic vaccines (which would cause the disease to regress or prevent dysplasia from progressing). Prophylactic vaccines that protect against HPV infection, if administered before the initiation of sexual activity, would prevent women from developing cervical cancer later in life. A therapeutic vaccine, theoretically, could help women already infected with HPV.

HPV immunization would offer a long-term solution to cervical cancer especially in developing countries, where it is especially difficult to effectively implement screening and treatment programs that reduce cervical cancer deaths. Both prophylactic and therapeutic approaches show promise, given the epidemiology and natural history of HPV-related disease, and natural immunity against HPV (Coursaget and Muñoz 1999; Duggan-Keen 1998; Lowy and Schiller 1998). Commercial vaccines are unlikely to be available for some years, and their effect on cervical cancer rates would not be measurable for years after their introduction. However, they have the potential to sharply reduce the incidence of cervical cancer (Jones 1999; Galloway 1998). For example, modeling of the clinical impact of vaccine introduction suggests that if a vaccine was introduced that was 98 percent effective against HPV type 16 and 18 infection, a 98 percent reduction in cancers associated with those two HPV types and a 51 percent reduction in total cancers could be expected, provided that coverage of the population of adolescent women was 100 percent (Goldie et al. 2003). An experimental vaccine targeting HPV type 16, which is associated with approximately half of all cervical cancers, is very promising. In a controlled trial the vaccine proved to be 100 percent effective in protecting against persistent HPV type 16 infections and associated precancerous cervical lesions (Koutsky et al. 2002).

When a commercial vaccine does become available, immunization programs will need to address the challenge of positioning the vaccine so that it will be acceptable to young women. A woman’s attitude about receiving an HPV vaccine is affected not only by her own risk behaviors but by such variables as knowledge of HPV, feelings about vaccinations in general, and perception that others approve of vaccination to affect (Kahn et al. 2003).

Although there is evidence that immune response does play a role in controlling HPV infections, it is not really known why HPV infections persist in some individuals and regress naturally in others (Duggan-Keen 1998; Galloway 1998). The distribution of HPV types varies substantially by geographic region. In Kenya, for example, the pattern of HPV types has been reported as different than in other regions, indicating that further research will be necessary to appropriately identify these regional differences in HPV prevalence (De Vuyst et al. 2003). Preventing a majority of cervical cancer cases therefore will require a multivalent vaccine that is effective against a combination of common HPV types (Galloway 1998).

Even with the most optimistic assumptions about when a prophylactic or therapeutic vaccine will become available, many hundreds of thousands of women will develop cervical cancer in the coming decades. Therefore, it is important to continue developing appropriate screening and treatment programs for precancerous lesions. For more information on HPV vaccine development, see PATH's paper *HPV Vaccines: Promises and Challenges* (www.path.org/resources/cxca_publications.htm).

Top of Page

Cervical cancer and HIV

Cervical cancer is an important AIDS-related disease in women. Since 1993, the disease has been considered an AIDS-defining illness in women infected with HIV. Studies have established a higher prevalence of HPV infection among HIV-positive women compared to HIV-negative women; women with HIV infection are at risk of more virulent HPV infections and more rapid progression from infection to neoplasia (Abercrombie and Korn 1998; Luque et al. 1999). HIV and HPV-infected women also are more likely to have dysplasia than women infected with either virus alone (La Ruche et al. 1998). Furthermore, there is evidence suggesting that the higher prevalence of HPV among HIV-seropositive women reflects persistence or reactivation of pre-existing HPV infection rather than recent acquisition of new infection (Palefsky 1999).

Cervical dysplasia is common in women with HIV infection; those who are more severely immunosuppressed appear to be at a higher risk for dysplasia and neoplasia (Leroy et al. 1999; Fruchter et al. 1998; Abercrombie and Korn 1998). Studies have found that the prevalence of dysplasia among HIV-infected women ranges from 31 to 63 percent, and HIV-positive women are almost five times more likely to have dysplasia than HIV-negative women. In addition to having a higher prevalence of cervical dysplasia, women with HIV tend to have larger lesions, more advanced dysplasia, and more vulvovaginal lesions than do HIV-negative women. Dysplasias can be persistent, progressive, recurrent, and difficult to treat in women with HIV (Abercrombie and Korn 1998; Tate and Anderson 2002). In addition, recent research suggests that vitamin A deficiency may play a role in the development of squamous intraepithelial lesions (SILs) in HIV-positive women (French et al. 2000). Less is known about the interaction between HIV and invasive cervical cancer. There is evidence to suggest that HIV-positive women with invasive cervical cancer are approximately 10 years younger than their counterparts who are HIV-negative (Gichangi et al. 2003). A large proportion of HIV-positive women with invasive cervical cancer may have acquired the infection after the start of abnormal cell changes (Fruchter et al. 1998). However, several studies in Africa suggest that although SILs (both low-grade and high-grade) are more common in HIV-positive women, the lesions may not advance to the invasive cervical cancer stage (Chirenje et al. 2002; La Ruche et al. 1998). This may be due, in part, to women succumbing to other HIV-related opportunistic infections before invasive cervical cancer develops (Chirenje et al. 2002).

The most effective methods of screening and treatment of dysplasia in HIV-infected women are under study. Current recommendations are to screen HIV-positive women every 6 months with a Pap smear and refer for colposcopy any women who has atypia or dysplasia on her Pap smear (Abercrombie and Korn 1998). Recent evidence has shown a dramatic increase in HIV shedding in HIV-positive women treated for precancerous lesions, highlighting the importance of abstaining from sexual intercourse while the cervix heals to reduce the risk of transmitting HIV to the partner (Wright et al. 2001).

Top of Page

Client perceptions

Research on how clients and health care providers perceive cervical cancer and the factors that contribute to client decisions to seek out cervical cancer screening treatment is crucial to the success of cervical cancer prevention programs. Many studies have shown that women in developing countries and other underserved populations lack information on cervical cancer and available services (Adanu 2002; Ajayi and Adewolfe 1998). Other factors reducing women's participation in cervical screening programs include poor awareness of the indications and benefits of the cervical smear test; lack of knowledge of cervical cancer and its risk factors, fear of embarrassment, pain, or cancer; anxiety caused by receiving an abnormal cervical smear result; and poor understanding of cervical screening procedures (Holroyd et al. 2004; Fylan 1998; Jameson et al. 1999). Women may face multiple barriers, including a lack of trust in health care providers, competing priorities due to extreme poverty, culturally biased attitudes toward cancer, and a general rejection of the pelvic exam (Lazcano-Ponce 1999; Masood 1999).

To overcome barriers such as these, studies have tried to assess various strategies for raising women's awareness of cervical cancer prevention and for increasing women's participation in screening programs. For example, a study in Brazil reported using interviews on a popular radio program, broadcasting messages by loudspeaker in neighborhoods, and having nurses visit homes to talk with women. Health center hours were flexible and available in the evenings and on weekends, and screening was offered in the woman's home if she could not get to the nearest health center (Mauad et al. 2002). A study in Mexico found that women who have had a positive prior experience with health services and providers were more likely to seek screening services. In areas where screening programs have low coverage, it may be beneficial to focus on improving the quality of care as a means of increasing utilization of screening services (Lazcano-Ponce et al. 2002). Other researchers are assessing whether using self-collection methods instead of pelvic examinations may make cervical cancer screening more acceptable to women. Self-sampling can be done in the woman's home, offering her increased privacy and less pain and embarrassment (Dzuba et al. 2002). (For more on self-sampling, see the section on the role of HPV tests, above.)

In recent years, there has been much interest in the psychological consequences of receiving an abnormal cervical smear and colposcopy. Studies have found that low levels of information, coupled with poor communication between patients and health professionals, contribute to high levels of negative psychological consequences (including emotional distress, uncertainty, and perceived inability) in women with abnormal cervical smear results (Fylan 1998; Lauver et al. 1999). These psychological consequences are associated with nonattendance and delay in seeking follow-up services for abnormal smear results. Clinical interventions that foster and promote coping strategies such as acceptance, relaxation, and diversion can help reduce psychological distress associated with the experience of having an abnormal smear result (Lauver et al. 1999).

Studies also show that health care providers are in need of effective technical training in cervical dysplasia screening/ treatment and training in educating and counseling clients at risk of cervical cancer (PATH 1996; Strickland et al. 1996.) Increased availability of better information and educational materials through a variety of channels may help reduce the anxiety and stress caused by receiving a positive Pap smear result (Idestrom et al. 2003). Successful intervention strategies to promote cervical cancer screening have included mass media campaigns, outreach programs, mobile examination rooms, and personalized letters to patient populations (Marcus and Crane 1998; Masood 1999; Tatum et al. 1997).

Top of Page

Cervical Cancer Prevention

- Program Examples
- Links
- Presentations
- Spanish Edition

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Annotated Bibliography

The entries below are organized under the major research areas used in the Key Issues section. Hint: use the Edit/Find function of your web browser to search for words in this page.

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
- Spanish Edition

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Annotated Bibliography

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General

Abwao, S. et al., eds. ***Prevention and Control of Cervical Cancer in the East and Southern Africa Region.*** Summary of proceedings of regional meeting held in Nairobi, Kenya, March 29–April 1, 1998.
The document provides summaries of the technical papers, the subsequent discussion sessions, and the country profiles. Action plans developed by the 15 country teams that participated, an overview of available funding and technical resources, and the consensus recommendations from the meeting are included.

Bishop, A. et al. **Cervical cancer: evolving prevention strategies for developing countries.** *Reproductive Health Matters* 6:60–71 (November 1995).
This article makes a strong case for rational, public health approaches to the prevention and treatment of cervical cancer, focusing on practical strategies that can be used in developing countries. The authors note that scarce resources, limited infrastructure, and competing health priorities have prevented most developing-country health systems from implementing successful programs. Three approaches to cervical cancer screening are suggested for programs with limited resources: (1) screening women aged 30–35 or older; (2) screening women relatively infrequently; and (3) considering alternate approaches to conventional screening techniques. For women identified as needing treatment, the authors discuss outpatient approaches, such as cryotherapy and loop electrosurgical excision procedure (LEEP), that can effectively treat most precancerous lesions and reduce the number of clinic visits. The authors recommend coordinating efforts to achieve broader screening and treatment coverage, and they note that introducing alternate approaches requires policy changes, for which community input is essential.

Fahey, M.T. et al. **Meta-analysis of Pap test accuracy.** *American Journal of Epidemiology* 141:680–689 (1995).
This meta-analysis examined 62 studies published by August 1992 that compared Papanicolau (Pap) test results with histology. Data from 59 of the studies were used to assess the accuracy of the Pap test. Estimates of Pap smear sensitivity ranged from 11 percent to 99 percent and estimates of specificity ranged from 14 percent to 97 percent. The authors found that a specificity in the 90 percent–95 percent range on a Pap test corresponds to a sensitivity in the 20 percent–35 percent range. While many studies had methodological weaknesses, the authors concluded that an increase in sensitivity almost always corresponded to a decrease in specificity or vice versa and that the Pap cannot achieve concurrently high sensitivity and specificity. They recommended that future studies follow methodological standards for diagnostic test evaluation more closely.

Fahs, M.C. et al. **Cost-effective policies for cervical cancer screening: an international review.** *Pharmacoeconomics* 3: 211–230 (March 1996).
This international review of the cervical cancer literature focuses on studies that address the cost-effectiveness of cervical cancer screening. The authors conclude that centrally organized screening programs implemented by the public sector are the most cost-effective type of program. Many programs are not effective (and have limited impact) due to over-screening of younger, affluent, lower-risk women and under-screening of older, less affluent, and minority women (for example, with opportunistic screening and screening at the discretion of individual health care practitioners). The authors also conclude that it is more cost-effective to begin screening women between the ages of 25 and 35. The appropriate cost-effective age to end screening is less clear; once an older woman has had several negative Pap smears, screening is less efficient and can be discontinued. The authors found that the interval of screening with the best balance between cost and life years saved was between 3 and 5 years. However, when repeat screening is not feasible, even one test per lifetime can significantly reduce mortality of a population. Efforts to reach unscreened women are particularly important as this population is typically at higher risk of developing cervical cancer. The authors noted three factors that can heavily impact the cost-effectiveness of a screening program: proportion of women screened by the program, quality of the Pap smear, and the cost of the Pap smear. Finally, the review discusses different cost models and analyses for evaluating cervical cancer screening and suggests the need for models that incorporate total costs and benefits of cervical cancer screening to society.

Hernandez-Avila, M. et al. **Evaluation of the cervical cancer screening programme in Mexico: a population-based case-control study.** *International Journal of Epidemiology* 27:1–7 (1998).
This case-control study evaluated the preventative effect of the cervical cancer screening program in Mexico City between September 1990 and December 1992. The authors selected 233 cases of cancer *in situ* and 397 cases of invasive cancer from women attending the gynecological clinics at six hospitals in Mexico City for histological confirmation following cytological diagnosis of cervical neoplasm. The 1,003 controls were an age-stratified random sample of residents of the Mexico City metropolitan area. When interviewed about their Pap smear history, cases were asked about the 12-month period before their diagnosis and controls were asked about the 12-month period before their interview. The authors found that the cervical cancer screening had a protective effect in relation to invasive cervical cancer. Women who had a history of a Pap smear, who did not seek screening due to gynecological symptoms, and who had received their Pap results had a 2.63 times lower risk of developing invasive cervical cancer (OR = 0.38; 95% CI = 0.28–0.52). No protective effect was found for *in situ* cancer. The authors note that the effect of the screening program is small when examined from a population perspective. They suggest that this results from low Pap-coverage (only 50 percent of those interviewed had ever had the test) and the high proportion of women who seek the test because they have symptoms.

Jones, S.B. **Cancer in the developing world: a call to action.** *British Medical Journal* 319:505–508 (August 1999).
This article synthesizes several themes from a 1999 WHO conference on "Cancer Strategies for the New Millennium." The author uses charts to characterize global cancer incidence by country, cancer type, incidence, and mortality rates. He notes that developing countries experience a disproportionate disease impact. For cancers with a known cause, such as cervical cancer, he recommends pursuing affordable approaches to prevention combined with development of new technologies appropriate to low-resource settings. The author also notes that clinical trials are underway for two prophylactic HPV vaccines and a therapeutic vaccine that stimulates cell immunity to viral proteins E6 and E7. Development of vaccines and low-technology approaches to detection offer the best promise for controlling cervical cancer in the developing world.

Parkin, D.M. et al. **Estimates of the worldwide incidence of 25 major cancers in 1990.***International Journal of Cancer* 80:827–841 (1999).
This comprehensive review of the worldwide burden of cancer estimates the annual incidence rates (crude and age-standardized) and numbers of new cases of 25 different cancers in 23 areas of the world as of 1990. In 1990, more than 371,000 new cases of cervical cancer were identified among women worldwide. Nearly 290,000 of these cases are estimated to have occurred in developing countries. The highest age-standardized incidence of cervical cancer in 1990 was reported in southern Africa, Central America, and Melanesia, where the rates were over 40 per 100,000 women. Rates of more than 30 per 100,000 were reported in eastern Africa, the Caribbean, and tropical South America. For a companion study of mortality from 25 cancers in 1990, see Pisani et al. 1999.

Parkin, D.M. and Sankaranarayanan, R. **Prevention of cervical cancer in developing countries.** *Thai Journal of Obstetrics and Gynaecology* 11 (Suppl. 1):3–20 (August 1999).

This article provides a review of methods available for preventing cervical cancer in developing countries. It describes the acceptance of the human papillomavirus (HPV) as the most important etiological agent and the difficulty involved in primary prevention of HPV. It describes the methods and difficulties involved with screening and early detection of cervical cancer through health education strategies and downstaging (which the authors conclude is not a cost-effective procedure). It also describes screening for pre-invasive disease through Pap smears, its effectiveness and difficulties in the organization of screening programs in developing countries, and visual inspection using acetic acid, which the authors report to be as sensitive as Pap tests, though generally less specific. Finally, the authors review testing for human papillomavirus, the value of which they conclude will have to await the development of tests that can be applied rapidly and relatively cheaply.

PATH (Program for Appropriate Technology in Health). **Preventing cervical cancer in low-resource settings.***Outlook* 18(1):1–8 (September 2000) (http://www.path.org/files/eol18_1.pdf).
This issue of *Outlook* describes the problem of cervical cancer in developing countries, the basic principles of cervical cancer control, screening and treatment options, and more.

Pisani, P. et al. **Estimates of the worldwide mortality from 25 cancers in 1990**. *International Journal of Cancer* 83:18–29 (1999).
This article presents worldwide estimates of annual mortality from all cancers and for 25 specific cancer sites from 1990. Crude and age-standardized mortality rates and numbers of deaths were computed for 23 geographical areas. The study estimated the global number of deaths from cervical cancer in 1990 at 190,000. Eighty percent of these deaths occurred in developing countries, where cervical cancer remains the largest cause of cancer death among women (followed closely by breast and stomach cancers). Some 40 percent of the estimated 148,500 cervical cancer deaths in developing countries occur in south central Asia, a region that includes India, Pakistan, Bangladesh, Afghanistan, and Iran, among others. For a companion study of worldwide cancer incidence in 1990, see Parkin et al. 1999.

Ponten, J. et al. **Strategies for global control of cervical cancer.** *International Journal of Cancer* 60:1–26 (1995).
This extensive review summarizes data from around the world on cervical cancer. Topics addressed include the tumor biology and natural history of cervical cancer, etiology of the disease (including impact of HPV), strategies for reducing mortality without screening (including focusing on treatment of early stage disease), and cytological screening. The authors conclude that the natural history and disease patterns of cervical cancer are similar throughout the world. They argue that HPV testing as a strategy for cervical cancer control remains experimental, and that providing treatment for early-stage disease where feasible can help reduce mortality. They discuss the challenges of ensuring maximum coverage with cytological screening without wasting resources on frequent testing of women at lower risk.

Rajkumar, R. et al. **Leads to cancer control based on cancer patterns in a rural population in South India.** *Cancer Causes and Controls* 11:433–439 (2000).
This study reviewed cancer patterns from the population-based cancer registry in Palani and Oddanchatram taluk in Dindigul District, Tamil Nadu State, South India. The Ambillikai Cancer Registry (ACR) records invasive and in-situ cancers for a rural population of 359,525 in 384 villages (estimate for 1996–1998). A total of 763 cancer cases were recorded during 1996–1998, 310 male and 473 female. In women, uterine cervical cancer accounted for more than half (53.9%) of all cases, with an age-specific and age-standardized rate of 65.4 cases per 100,000 person years. This age-standardized rate is the second highest in the world, following a rate observed in Harare, Zimbabwe (67.2). The age-specific rate for women ages 40 to 60 years from the ACR is the highest in the world. More than four-fifths of the cervical cancer cases from the ACR were diagnosed in FIGO stages IIB and IIIB. It is possible that the true risk for cervical cancer is even higher, since cases in old age groups may be under-registered. Breast and mouth cancers were the second and third most common cancers among women (age-standardized rate of 14.2 and 10.2 respectively). For men, mouth cancer was the most commonly recorded cancer (age-standardized rate: 11.5), followed by tongue (age-standardized rate: 8.6), hypopharynx (age-standardized rate: 7.8), esophagus (age-standardized rate: 7.8), and larynx (age-standardized rate: 7.8).

Rogo, K.O. et al. **Carcinoma of the cervix in the African setting.** *International Journal of Gynecology and Obstetrics* 33:249–255 (1990).
Data on 1,210 patients treated in Kenya between 1974 and 1979 formed the basis for this study. The authors compared Kenyan data to statistics for cervical cancer incidence in developed countries and found Kenyan patients to be both younger (mean age 42 versus 54 years) and more likely to present with late-stage disease (55% Stage 3 compared to 25%). A high loss to follow-up and limited treatment resources contributed to poor survival outcomes. The authors cited some possible additional contributors to high mortality, including tumor bulk, nutrition, and individual immunity. They concluded that further study of the differences in findings is needed and noted that cytologic screening is less likely to succeed in developing country settings.

Sherlaw-Johnson, C. et al. **Evaluating cervical cancer screening programmes for developing countries.** *International Journal of Cancer* 72(2):210–216 (July 1997).
This study evaluates infrequent cervical screening and programs in which as many women as possible are screened just once in their lifetime in developing countries. It also compares the effectiveness of cytology and HPV testing for primary screening. Evaluation criteria

include: progression of precancer by use of a stochastic model, its relationship to HPV infection, and diagnostic accuracy of alternative screening methods. These criteria are compared in terms of the impact on the incidence of invasive cancer and resource use. The authors found that blanket screening for women aged 30–59 years, with the aim of covering all just once in their lifetime, could reduce the incidence of invasive cancer by up to 30 percent. The effectiveness of cytology and HPV testing as a primary screening method depends on the underlying prevalence of HPV infection, the accuracy of cytology, the cost and the suitability of the testing procedure under field conditions.

Sherris, J.D. **Cervical cancer prevention: a strategic opportunity to improve women's reproductive health.** *International Family Planning Perspectives* 25 (Suppl.):556–557 (1999).
This article summarizes the issues associated with preventing cervical cancer in developing countries and the steps needed to strengthen prevention efforts. The article also reports the initial findings of the Cervical Cancer Consultative Group, which in 1997 identified a list of ten questions felt to be of highest priority in guiding strategy development for preventing cervical cancer in low-resource settings. The author concludes by stating that activities focused on answering these questions will contribute to preventing some of the 200,000 deaths from cervical cancer that occur each year in developing countries.

Top of page

Epidemiology and natural history of cervical cancer

Anttila, T. et al. **Serotypes of *Chlamydia trachomatis* and risk for development of cervical squamous cell carcinoma.** *Journal of the American Medical Association* 285(1):47–51 (January 3, 2001).
This study and the accompanying editorial by Zenilman, J.M. provide evidence that *Chlamydia trachomatis* is associated with an increased risk for developing cervical cancer. This study reports on data from a longitudinal, nested case-control study in a cohort of 530,000 serum samples from women in Finland, Norway, and Sweden. Invasive cervical cancer was identified in 181 women through linked records to national cancer registries. *C. trachomatis* has 18 different serotypes. Of these the highest risk of cervical cancer was associated with serotype G (adjusted odds ratio 6.6, 95 percent confidence interval (1.6–27.0). Serotype I and D and exposures to multiple serotypes were also found to be associated with an increased risk of subsequent development of cervical cancer.

Biswas, L.N. et al. **Sexual risk factors for cervical cancer among rural Indian women: a case-control study.** *International Journal of Epidemiology* 26(3):491–495 (June 1997).
This hospital-based case-control study in India investigates the role of sexual risk factors in cervical cancer among rural women with a low rate of sexual promiscuity. The study included 134 women with invasive cervical cancer and 134 control women. Results from multiple logistic regression analysis showed that cervical cancer is associated with early age at first coitus, extramarital sex partners, and the time interval since first exposure. Independent effects were observed for early age at first coitus. Women who reported their first intercourse at less than 12 years of age were at the greatest risk compared to that of their counterparts at 18 years or older. Increased risk was also observed for women who had extramarital sex partners. The findings confirm the association between early age at first coitus and cervical cancer in women with a low rate of sexual promiscuity.

Bosch, F.X. et al. **Prevalence of human papillomavirus in cervical cancer: a worldwide perspective.** *Journal of the National Cancer Institute* 87(11):796–802 (June 7, 1995).
This study confirmed an extensive, global association between human papillomavirus (HPV) infection and cervical cancer. The study had two objectives: to determine whether the association between cervical cancer and HPV was consistent worldwide and to investigate geographic variation in the distribution of over 20 types of cancer-associated HPV. Investigators collected more than 1,000 specimens from cervical cancer patients in 22 countries with high recorded cervical cancer incidence. HPV DNA was detected in 93 percent of the tumors. Although HPV types differed somewhat by geographic region, HPV 16 was present in 50 percent of all specimens. The second most predominant type, HPV 18, was present in 14 percent of all specimens.

Brinton, L.A. **Epidemiology of cervical cancer—an overview.** In: *The Epidemiology of Cervical Cancer and Human Papillomavirus*, Muñoz, N. et al., eds. Lyon: International Agency for Research on Cancer. Scientific Publication Number 119, 3–23 (1992).
Numerous studies of cervical cancer epidemiology are reviewed in this 1992 publication that examines factors other than HPV associated with cervical cancer. In tables summarizing findings from multiple studies, the author demonstrates the strong association between cervical cancer risk and number of sexual partners and age at first intercourse (which may be markers for HPV risk). She then examines epidemiologic evidence for contributory or interactive roles of other suspected risk factors, such as the relationship between HPV and other sexually transmitted diseases. She reviews study findings for more speculative risk factors also, particularly cigarette smoking and use of oral contraceptives. She concludes by noting that disease risk may be affected by changes in recent times including the tendency for women to initiate sexual intercourse at earlier ages, increased exposure by younger women to cigarette smoking and oral contraceptives, and changes in the sexual behavior of their male partners.

Burk, R.D. **Pernicious papillomavirus infection [editorial].** *New England Journal of Medicine* 341(22):1687–1688 (November 25, 1999).
In this editorial, the author reviews some of the evidence that HPV causes cervical cancer. While not all of the criteria proving causation have been established, cervical cancer begins with sexual transmission of HPV to a woman susceptible to persistent infection. A study by Wallin et al. in the same issue found that HPV was present in the Pap smears of most women who later developed cervical cancer. This study also found a relatively high rate of false-negative Pap smear results, which the author notes is cause for concern. The author concludes that it may be time to consider periodic HPV screening along with Pap smears, especially for older women at high risk for high-grade cervical disease.

Critchlow, C.W. and Kiviat, N.B. **Old and new issues in cervical cancer control (editorial).** *Journal of the National Cancer Institute* 91 (3):200–201 (February 3, 1999).
This editorial comments on the Holowaty et al. article on natural history and supports the practice of following women with cytologic diagnosis of mild dysplasia rather than immediate referral for colposcopy and biopsy. The authors note that the Holowaty et al. results confirm the results of previous studies that indicate that most mild and moderate dysplasia regresses spontaneously. Given the methodological rigor of the study, Holowaty et al.'s results add strength to earlier findings. The editorial also comments on the Palefsky et al. study of HPV infection in HIV-positive and HIV-negative women, which showed that HIV-positive women are at markedly increased risk of HPV infection (probably reactivated latent infection), particularly with high-risk HPV types.

Gustafsson, L. et al. **International incidence rates of invasive cervical cancer after introduction of cytological screening.** *Cancer Causes Control* 8(5):755–763 (September 1997).
This study compares the changes in cervical cancer incidence at different ages after the introduction of cytologic screening in different populations, and addresses the impact of organized and opportunistic smear taking. The relative reduction in age-specific incidence rates and in incidence rates age-standardized to the world population after the introduction of screening were calculated for each of the 17 cancer registries identified. In 11 of the 17 populations, age-standardized incidence rates declined markedly, from 27 percent in Norway to 77 percent in Finland. Age-specific declines were confined to women aged 30 to 70 years old; incidence rates were lowest among women aged 40 to 55. The authors state that because age-specific declines in cervical cancer incidence rates were strikingly similar in populations with widely different screening practices, organized screening may not be markedly superior to opportunistic screening.

Ho, G.Y. et al. **Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia.** *Journal of the National Cancer Institute* 87(18):1365–1371 (September 20, 1995).
This study analyzed the factors that determine cervical intraepithelial neoplasia (CIN) persistence or regression and found that persistent CIN is linked to chronic HPV infection, particularly HPV infection with a high viral load. The study enrolled 100 U.S. women diagnosed with CIN II. About one third of the women experienced regression; the remaining 70 were evaluated at three-month intervals for 15 months. Women who had chronic HPV infection had a fourfold higher risk for persistent CIN than those without HPV. The authors noted that repeated testing for HPV infection may help clinicians to differentiate between women who are likely to experience spontaneous regression and women whose lesions will persist or progress.

Holowaty, P. et al. **Natural history of dysplasia of the uterine cervix.** *Journal of the National Cancer Institute* 91(3):252–258 (February 3, 1999).
This article reviews a historical cohort of women in Toronto, Canada, whose Pap smear histories were recorded at a major cytopathology laboratory. This authors studied progression and regression of cervical dysplasia in this cohort during the period 1962 to 1980. The cohort size and time period covered by the analysis distinguishes this study from others, which tend to be much smaller and of shorter duration (the article includes a useful summary table illustrating the results of previous studies). The results of the study confirm those of smaller studies: the risk of mild dysplasia progressing to cervical cancer *in situ* (CIS) is small—about 1 percent per year. The study results support the recommendation of following patients with mild dysplasia with periodic cytology rather than immediate referral to colposcopy. The study also found that the risk of moderate dysplasia progressing to CIS is intermediate between the risks associated with mild and severe dysplasia—16 percent in 2 years.

Kjaer, S.K. et al. **Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in younger women: population based prospective follow up study.** *British Medical Journal* 325(7364):572 (September 14, 2002). Available at: http://bmj.bmjjournals.com/cgi/content/full/325/7364/572?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&searchid=1063662947341_14425&stored_search=&FIRSTINDEX=0&sortspec=relevance&volume=325&firstpage=572&resourcetype=1,2,3,4,10.)
Much of what is known about HPV infection and the development of cervical neoplasia is drawn from cross-sectional studies and a few prospective cohort studies. The authors of this study conducted a population-based prospective study that followed 10,758 women between 20 and 29 years of age. Cervical smears and cervical swabs for HPV DNA testing were taken at enrollment and at a two-year follow-up visit. In the final study population, consisting of 653 women with normal cytology, and 252 incident cases of cervical dysplasia

(25 atypical cells, 115 low-grade lesions, and 112 high-grade lesions), HPV 16 was the most common HPV type detected. For women who had normal cytology at enrollment, but who subsequently developed high-grade lesions, 80 percent were also HPV-positive at enrollment. Among women who had normal cytology but were HPV-positive at their first exam, 71 percent (62/87) cleared the infection by the second exam (45 became HPV-negative, 17 cleared that specific type of HPV but acquired a different HPV type). The study found an increased risk of developing cervical lesions for women who were HPV-positive at enrollment and at the follow-up visit. The most pronounced risk was for women with high-grade lesions who were HPV-positive at both exams as compared to women who were HPV-negative at both exams (odds ratio 413.9, 96.3 to 1779.5). The odds ratio increased most substantially for women with high-grade lesions who were positive with the same HPV type at both exams as compared to HPV negative women (odds ratio 813, 168.2 to 3229.2), suggesting that persistent infection with a high risk HPV type is a good predictor of subsequent high-grade lesions.

Kjellberg, L. et al. **Smoking, diet, pregnancy and oral contraceptive use as risk factors for cervical intra-epithelial neoplasia in relation to human papillomavirus infection.** *British Journal of Cancer* 82:1332–1338 (2000).
This study sought to distinguish if smoking, nutrition, parity, and oral contraceptive use are independent risk factors for cervical cancer, or whether they may act as cofactors with human papillomavirus (HPV) infection. This population-based case-control study was undertaken in the Västerbotten county of Northern Sweden of 137 women with high-grade cervical cancer (CIN II or III) and 253 healthy age-matched women. The women completed a 94-item questionnaire, and donated specimens for HPV testing. Of the environmental risk factors being studied, smoking appeared to be a significant risk factor for cervical cancer. Smoking was associated with CIN II–III (odds ratio 2.6, 95 percent confidence interval of 1.7–4.0), and was dose-dependent. The excess risk was not affected by adjusting for HPV infection, suggesting that smoking is a causal risk factor for CIN II–III. The study did not find diet to be protective (as other studies had suggested). Pregnancy appeared to be a risk factor for CIN II–III, and further study is warranted. Prolonged oral contraceptive use and sexual history were not associated with CIN II–III when HPV infection was taken into account.

Lancaster, E.J. et al. **Carcinoma of the uterine cervix: results of Ka-Ngwane screening programme and comparison between the results obtained from urban and other unscreened rural communities.** *East African Medical Journal* 76(2):101–104 (February 1999).
This study revived data from 10,000 consecutive Pap smears from women attending Ob/Gyn clinics in Ka-Ngwane, Pretoria (urban area), and Transkei (rural area) in South Africa. The study found positive Pap smears (mild dysplasia through cancer) in 3 percent of patents in Ka-Nguane, 5 percent in Greater Pretoria, and more than 6 percent in Transkei. Of the positive cases, cervical cancer accounted for 12 percent of cases in Ka-Ngwane, 5 percent in Pretoria, and 26 percent in Transkei. The majority of positive cases were younger than 41 years (the article did not indicate the age distribution of all 10,000 patients). The authors concluded that there is a high incidence of dysplasia and cervical cancer in previously unscreened populations in South Africa, and that there is an urgent need to develop education and screening programs in the region. The authors also noted that a significant proportion of cervical cancer cases occurred in women below 40 years of age.

Li, H.Q. et al. **The decline in the mortality rates of cervical cancer and a plausible explanation in Shandong, China.** *International Journal of Epidemiology* 29:398–404 (2000).
This study analyzed the decline in cervical cancer deaths in Shandong Province, China, from 1970 to 1992. China has had one of the most rapid declines in the incidence of cervical cancer of any Asian country. This is largely due to social changes and health policies put in place by the Chinese government after the 1949 founding of the People's Republic of China. These changes reduced exposure to sexually transmitted diseases; they also resulted in improved screening and treatment. Lifetime exposure to risk factors and co-factors (such as smoking) declined with successive birth cohorts. The authors conclude that if the recent increase in rates of sexually transmitted diseases continues in China, an increase in rates of cervical cancer is likely to follow.

Moreno, V. et al. **Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infections: the IARC multicentric case-control study.** *Lancet* 359:1085–1092 (March 30, 2002).
This study analyzed data from a large multi-center cancer registry. Cases were matched with hospital-based controls in five countries and population-based controls in two countries. Women were questioned about their life-long use of oral contraceptive pills (OCPs); however, no information was gathered on the type or dosage. HPV infection was determined using PCR. Analysis by logistic regression adjusted for confounders and results showed that HPV positive women who had ever used OCPs were 1.5 times more likely to develop cervical cancer than controls. Women who used OCPs for 5–9 years had a significant association with cervical cancer (odds ratio, 2.82; 95% CI = 1.46–5.42). Comment by David Skegg (*Lancet* 359:1080–1081) discusses study weakness that make interpreting the data complex. These shortcomings include possible recall bias, lack of distinction between OCPs and other hormonal contraceptives, small number of HPV-positive controls, and the use of logistic regression analysis when controlling for confounding factors.

Moscicki, A., Hills, N., Shiboski, S., et al. **Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females**. *Journal of the American Medical Association* 285(23):2995–3002 (June 20, 2001).
Results from the longest longitudinal study of incident human papillomavirus infection (HPV) reveal that, over a period of 36 months, 55 percent of women without prior HPV infection acquired an incident HPV infection. Associated risks for incident HPV infections, as indicated by multivariate analysis, include sexual behavior, smoking, prior herpes simplex virus infection, and history of vulvar warts. A woman’s risk of HPV infection increased 10-fold with each new sexual partner per month. Current oral contraceptive use provided a

significantly protective effect, though other literature has suggested a long-term increased risk of developing cervical lesions among oral contraceptive users. Consistent with previously reported findings by the authors, the results indicate that approximately 90 percent of young women clear the HPV virus within 36 months. Findings from this study shed light on the time between HPV infection to the development of low-grade SILs. Seventy percent of women with HPV infection, followed for 60 to 80 months, did not develop LSIL and the majority of women who did develop LSIL had the lesions spontaneous clear later.

Muñoz, N. et al. **Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study.** *Lancet* 359:1093–1101 (March 30, 2002).
This multi-center study pooled data on HPV-positive women to evaluate the association between parity and increased risk of cervical cancer. HPV infection was determined using PCR. Using logistic regression analysis to calculate pooled odds ratios, the authors reported a significant association between high parity and increased risk of squamous-cell cervical cancer. The association was strongest for women with seven or more full-term pregnancies (odds ratio, 3.8; 95% CI 2.7 to 5.5). For women with one or two full term pregnancies, the odds ratio was 2.3 (95% CI = 1.6 to 3.2). Comment by David Skegg (*Lancet* 359:1080–1081) outlines several weaknesses that should be kept in mind when interpreting the data. These shortcomings include the use of hospital-based controls, small number of HPV-positive controls, and the use of logistic regression analysis when controlling for confounding factors.

Nasiell, K. et al. **Behavior of mild cervical dysplasia during long-term follow-up.** *Obstetrics and Gynecology* 67(5):665–669 (May 1986).
This Swedish study evaluated follow-up data from 555 women diagnosed with mild cervical dysplasia between 1962 and 1983. Of these mild dysplasias, 62 percent regressed, 22 percent persisted, and 16 percent progressed. Patients with regression were followed for an average of 39 months; patients with persistent dysplasia were followed for an average of 52 months. Where mild dysplasia progressed to more severe disease, the average time to progression was 48 months. Two cases of invasive cancer occurred in women lost to follow-up for several years during the study. The invasive cancers were diagnosed at 79 and 125 months after initial diagnosis of mild dysplasia. This study is often cited as evidence that a significant proportion of mild dysplasia does not progress to more severe disease. At the same time, the study results highlight the importance of regular follow-up of women diagnosed with mild dysplasia, given the potential of progression in more than a sixth of cases.

Pisani, P. et al. **Cancer and infection: estimates of the attributable fraction in 1990.** *Cancer Epidemiology, Biomarkers, and Prevention* 1:387–400 (June 1997).
This article, written by researchers from the International Agency for Research on Cancer (IARC), reviews the evidence linking various cancers to infectious agents, including cervical cancer and HPV infection. The article includes data from around the world, and concludes that over 90 percent of cervical cancer cases in the developing world can be directly attributed to HPV infection.

Prokopczyk, B. et al. **Identification of tobacco-specific carcinogen in the cervical mucus of smokers and nonsmokers.** *Journal of National Cancer Institute* 89(12):868–873 (June 18, 1997).
The goal of this study was to determine for the first time whether tobacco-specific carcinogen N-nitrosamines (NNK) are present in the cervical mucus of cigarette smokers and of nonsmokers. Cervical mucus specimens from 15 smokers and 10 nonsmokers were tested for NNK. NNK was found in all cervical mucus specimens of smokers, and only one nonsmoker specimen did not contain detectable NNK. NNK concentrations in specimens from cigarettes smokers (11.9 to 115.0 ng/g of mucus) were significantly higher than those from nonsmokers (4.1 to 30.8 ng/g of mucus). The authors suggested that the presence of NNK in the cervical mucus of nonsmokers is likely due to environmental exposure or to the fact that some of the women in the study may not have revealed that they occasionally smoked cigarettes. The finding of this study further strengthens the association between cervical cancer and tobacco smoking.

Robles, S.C. et al. **Trends in cervical cancer mortality in the Americas.** *Bulletin of PAHO* 30(4):290–301 (1996).
This article provides an assessment of cervical cancer mortality trends in the Americas using data from the Pan American Health Organization. While cervical cancer in Canada and the United States has declined steadily over the past 30 years (to about 1.4 and 1.7 deaths per 100,000 women, respectively, in 1990), most Latin American and Caribbean countries with available data have experienced constant or increasing levels of cervical cancer mortality (generally in the range of 5 to 6 deaths per 100,000 women). The authors suggest that while not all changes in cervical cancer mortality can be directly attributed to screening, a correlation clearly can be drawn. They suggest that screening services in Latin America have been linked to family planning and prenatal care services, and have not appropriately targeted older women with the highest risk of cervical cancer.

Roteli-Martins, C.M. et al. **Cigarette smoking and high-risk HPV DNA as predisposing factors for high-grade cervical intraepithelial neoplasia (CIN) in young Brazilian women.** *Acta Obstetrica et Gynecologica Scandinavica* 77:678–682 (1998).
This cross-sectional study of young Brazilian women aged 20–35 investigated the role of cigarette smoking and high risk HPV types as risk factors for CIN 2 and 3. The study included 77 women with biopsy confirmed CIN 1, 2, and 3. Women with CIN 1, 2, and 3 did not differ significantly from one another with regard to age, race, schooling, marital status, lifetime number of sexual partners, age of first intercourse, use of oral contraceptives, or parity. Results from multivariate logistic regression analysis, however, showed that smoking

and HPV type were significantly associated with CIN 2 and 3. Smoking increased the risk of developing CIN 2 and 3 by 6.6 fold and the detection rate of high-risk HPV types was significantly higher among cigarette smokers than among nonsmokers. These findings indicate the relationship between severe CIN lesions and both high-risk HPV types and current cigarette smoking. They also suggest that there may be a synergistic action between these two factors in the development of cervical cancer.

Schiffman, M.H. **New epidemiology of human papillomavirus infection and cervical neoplasia.** *Journal of the National Cancer Institute* 87(18):1345–1347 (September 20, 1995).
This article discusses the link between persistent detection of HPV DNA (especially high levels of DNA) and persistent diagnosis of CIN. A companion study by Ho et al. in the same journal issue tracked HPV and CIN transience versus persistence, and Schiffman notes that the findings of Ho et al. have implications for the development of screening strategies that include HPV-DNA testing. The author notes several findings and factors that complicate epidemiologic analysis: (1) HPV-negative CIN does exist, although it occurs in 10 percent or fewer cases; (2) up to 10 percent of women may develop CIN2 or CIN3 lesions initially instead of progressing from lower- to higher-grade lesions; (3) diagnostic uncertainty and the lack of a reference standard complicate interpretations of data; (4) the cervix may contain discrete lesions with separate natural histories (for example, CIN1 lesions may progress to CIN3 over time or simply emerge adjacent to CIN3 lesions).

Sellors, J.W. et al. **Prevalence of infection with carcinogenic human papillomavirus among older women.** *Canadian Medical Association Journal* 167(8):871–873 (2002).
Researchers obtained results of HPV DNA testing from 154 women over the age of 50 living in Ontario, Canada. This study investigated the prevalence of carcinogenic HPV in older women and the associated risk factors. In this study, HPV prevalence peaked for women older than 60 years. These findings also are consistent with another study of the natural history of HPV among Costa Rican women that found a high prevalence peaking in women older than 59 years. Risk factors that have a significant association to HPV infection in the Canadian study include the absence of a stable sexual partnership and early age at first intercourse.

Smith, J.S. et al. **Herpes simples virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer.** *Journal of the National Cancer Institute* 94(21):1604–1612 (November 6, 2002).
This article examined the association between herpes simplex virus-2 (HSV-2), HPV, and the development of invasive cervical cancer. Authors conducted a pooled analysis of seven case-control studies conducted in Morocco, Brazil, Peru, Columbia, Thailand, Philippines, and Spain. The pooled analysis examined a total of 1,263 patients with invasive cervical cancer and 1,117 controls to determine whether HSV-2 plays a role as a cofactor, in conjunction with HPV infection, to increase the risk of developing cervical cancer. Results showed that women with invasive cervical cancer had a higher rate of HSV-2 infection (44%) compared to women in the control group (26%). Women who were HPV-positive, infection with HSV-2 was associated with increased the risk of invasive cervical cancer. The authors conclude that while persistent HPV infection is still the strongest predictor of subsequent development of invasive cervical cancer, infection with HSV-2 may increase the risk.

Sukvirach, S. et al. **Population-based human papillomavirus prevalence in Lampang and Songkla, Thailand.** *Journal of Infectious Disease*s 187(8):1246–1256 (April 15, 2003).
There is a need for population-based, age-specific and type-specific regional data on HPV prevalence to further help define strategies for cervical cancer prevention. This study reports the results of 2 population-based prevalence surveys conducted as part of the International Agency for Research on Cancer's multicenter study on global prevalence of HPV infection. Overall, the prevalence of HPV DNA was 6.3 percent, although Lampang had a significantly higher HPV prevalence (8.0%; 95% CI = 6.4–9.8%) than Songkla (3.8%; 95% CI = 2.5–5.5%). The most frequently reported HPV types were 16, 52, and 72. Similar to other population-based surveys, women less than 35 years of age had the highest HPV prevalence (9.8%). HPV prevalence then remained stable, between 4.5 and 6.0 percent for women ages 35 years and older. HPV infection was statistically significantly associated with having previously had a sexually transmitted infection (odds ratio [OR], 3.2) or having Herpes simplex virus 2 (HSV-2) (OR, 2.1). HPV infection also appeared related to a woman's husband's sexual behaviors. For example, the risk of HPV DNA detection was higher for women who reported their husband had other sexual partners (OR, 1.9) or had sexual relations with prostitutes (OR, 1.6). The authors note that the lower than expected HPV prevalence may be due to a large number of younger women refusing to participate in the study because of the need for a pelvic exam and the fact that 85 percent of women reported only having had one sexual partner in their lifetime.

Thomas, D.B. et al. **Prostitution, condom use, and invasive squamous cell cervical cancer in Thailand.** *American Journal of Epidemiology* 143(8):779–86 (1996).
This article reports on a case-control study conducted in three hospitals to investigate the role of male sexual behavior in the development of cervical cancer in their wives. Data were obtained from interviews with 225 married women with invasive cervical cancer, 791 hospitalized controls, and from interviews with their husbands. The study found that the rise of cervical cancer was strongly related to the women's husbands having visited sex workers without using a condom when the husbands were less than 30 years old. The authors conclude that regular condom use by sex worker clients could reduce the number of invasive cervical cancer cases in Thailand's general population by at least 25 percent.

Wallin, K.L. et al. **Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer.** *New England Journal of Medicine* 341(22):1633–1638 (November 25, 1999).
This study compared Pap smear results from routine screening of Swedish women during the years 1969 to 1995. The authors compared normal smears in 118 women who later developed cervical cancer to the smears of 118 age-matched women who did not develop cancer. HPV DNA was detected in 30 percent of the smears of women with cancer, and in only 3 percent of those who remained healthy. At the time of diagnosis with cancer, 77 percent of the tissue samples tested positive for HPV DNA, while 4 percent of the matched controls were HPV positive. The HPV-DNA type was the same in the baseline smear and in the tissue sample for all of the women with cancer, but not for any of the healthy women (controls). While there is some concern that stored samples may underestimate the proportion of women who were HPV positive before developing cancer, the authors conclude that HPV DNA in normal Pap smears is associated with an increased risk for cervical cancer, and persistence of HPV infection is related to the development of cancer.

Zenilman, J.M. **Chlamydia and cervical cancer: a real association?** *Journal of the American Medical Association* 285(1): 81–83 (January 3, 2001).
This editorial accompanies Anttila et al. (2001) with a discussion of the evidence for an association between *Chlamydia trachomatis* and cervical carcinoma. The author states studies prior to the large multi-center study conducted by Anttila et al. have been weak methodologically and have been unable to adjust for confounders. The author interprets the Anttila et al. findings as providing strong evidence for a causal relationship between *C. trachomatis* and subsequent cervical cancer development. The author poses several questions for future research on the biological mechanisms and suggests that cervical cancer be considered a potential adverse outcome of Chlamydia infections.

Top of page

Role of HPV tests in cervical cancer prevention

Bollen, L.J. et al. **Human papillomavirus deoxyribonucleic acid detection in mildly or moderately dysplastic smears: a possible method for selecting patients for colposcopy.** *American Journal of Obstetrics and Gynecology* 177(3):548–553 (September 1997).
The goal of this study was to determine whether human papillomavirus testing is capable of discriminating between high- and low-grade squamous intraepithelial lesions so as to be useful in reducing the number of colposcopic examinations. One hundred and ninety women with smears of mild or moderate dysplasia were tested for presence of HPV DNA using the CPI/IIG and MY09/11 tests. The HPV test results were compared with histologic diagnosis, the reference standard. The study found that 56 of the 190 women had high-grade squamous intraepithelial lesions. The sensitivity was 96 percent for the CPI/IIG test and 95 percent for the MY09/11 test; specificity was 33 percent and 40 percent, respectively. The authors concluded that use of HPV tests as a secondary triage in women with mild or moderate dysplasia could prevent those women from undergoing unnecessary colposcopy.

Clavel, C. 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.** *British Journal of Cancer* 80(9):1306–1311 (1999).
Hybrid Capture II (HC-II) is an HPV-detection test designed to detect 18 high-risk and low-risk HPV types. This study evaluated how effective the HC-II test is for assessing high-grade cervical lesions as compared with cytological screening. Twenty-four percent of the samples taken from women attending routine cytological screening tested positive for HPV: 18 percent for high-risk types and 6.3 percent for low-risk HPV types. High-risk HPV was found in all of the cases presenting a high-grade lesion confirmed by biopsy. The overall sensitivity of the HC-II in detecting high-grade SILs and cervical cancers is 98.1 percent, and the specificity is 85.2 percent in cervical samples. Cytological testing was more specific (94.9%), but less sensitive (85.3%) in detecting high-grade SILs. The use of HC-II along with cytological screening would accurately diagnose most all high-grade lesions.

Cuzick, J. **Human papillomavirus testing for primary cervical cancer screening [editorial]**. *JAMA* 283(1);108–109 (January 5, 2000).
This editorial reviewed two articles appearing in the January 5, 2000 *JAMA* issue, Schiffman et al. and Wright et al. The editorial noted that the two articles made important contributions to assessing use of HPV for primary screening for cervical cancer. The Schiffman article focused on performance of HPV-DNA testing according to different thresholds of test positivity (a test using a 1 pg/mL cutoff for HPV positivity performed best) and according to patient age (specificity was highest for test results among older women). The Wright study evaluated results of HPV-DNA testing in an unscreened population using self-collected and clinician-collected samples. While the self-collected samples resulted in lower sensitivity than the clinician-collected samples, sensitivity was higher than Pap smear testing in that setting. Specificity remained a problem, however. The author concluded that HPV-DNA testing has significant potential for making cervical cancer screening available in settings where traditional approaches may not be feasible. Further study is necessary to clarify optimal approaches that will ultimately lead to reduced morbidity and mortality.

Denny, L. et al. **Evaluation of alternative methods of cervical cancer screening for resource-poor settings.** *Cancer* 89(4):826–833 (August 15, 2000).

This study compared the performance of four methods of screening for cervical cancer and precancerous lesions. Conventional cytology (Pap smear), direct visual inspection after an acetic acid wash (DVI), HPV-DNA testing, and cervicography were applied in sequence to 2,944 women in a resource-poor settlement outside of Cape Town, South Africa. After adjusting for loss to follow up, calculations were done similar to standard measures of sensitivity and specificity. Of the 2,944 women, 842 (29%) tested positive by one or more of the tests. Colposcopy and cervical biopsies were performed on 790 (90%) of the women testing positive. Overall test performance was best for cytology, which correctly identified approximately 78 percent of women with SIL or invasive cervical carcinoma (confirmed by biopsy). For women whose Pap smear was classified as normal or ASCUS, 97 percent were classified as negative by DVI, HPV-DNA testing, cervicography, and/or colposcopy. DVI and HPV testing using a standard cutoff level (RLU>1x positive control) had similar sensitivities to detect high-grade SIL and invasive carcinoma to cytology. The specificity of DVI, HPV testing, and cervicography, however, was much lower than cytology, and resulted in many more false-positives. The authors conclude that DVI and HPV-DNA testing have adequate sensitivities to make them effective tests for identifying women with cervical disease in low-resource settings (that is, in the absence of colposcopic evaluation). The authors caution that because these two tests identify considerably more women as having disease who are really disease free, the impact of providing immediate treatment of women based on the results of either DVI or HPV-DNA testing warrants further investigation.

Elfgren, K. et al. **A population-based five-year follow-up study of cervical human papillomavirus infection.** *American Journal of Obstetrics and Gynecology* 183(3):561–567 (2000).
This study reviewed results from a population-based cervical screening program in Sweden in 1991 to determine the persistence of cervical HPV DNA. Women with normal Pap smears but who tested positive for HPV DNA were age-matched with controls (women with normal cytology, absence of HPV DNA) and both groups were reexamined five years later. Of the women infected with HPV DNA in 1991, only four showed infection with the same type of HPV five years later. All of these women had HPV 16. This represents a five-year HPV clearance rate of 92 percent. Eleven women acquired HPV infection during the five-year follow-up period. Although this study did not attempt to compare HPV-DNA tests, it noted differences between the MY09 and MY11 and the GP5+ and GP6+ primer systems for detection of different types of HPV. Because of the high likelihood that HPV infection will clear spontaneously, the authors conclude that a single HPV screening test is of limited value. Strategies that rely on repeated HPV testing to identify persistent infections will be more cost-effective.

Hernandez-Avila, M. et al. **Human papilloma virus 16-18 infection and cervical cancer in Mexico: a case-control study.** *Archives of Medical Research* 28(2):265–271 (1997).
The goal of this case-control study was to evaluate the association between HPV types 16 and 18 and cervical cancer in women living in Mexico City. In the study, 148 cases and 204 controls were tested for HPV types 16 and 18 using polymerase chain reaction (PCR) technique. HPV 16 was detected in 48.3 percent of 60 *in situ* cases, 48.8 percent of 88 invasive cases, and 13.2 percent in controls. HPV 18 was detected only in 6.7 percent of invasive cases. The odds ratio for HPV 16 infection in *in situ* cases was 5.17 and the odds ratio for invasive cases was 3.84. The results showed that all women with a strong positive PCR reaction had the greatest risk; the odds ratio was 38 compared to 23 and 11 of intermediate and weak PCR reactions respectively. The finding provided further evidence for the association between HPV types 16 and 18 infection and cervical cancer. The authors considered that the Pap test is still the single most effective measure in cervical cancer control.

Hillemanns, P. et al. **Screening for cervical neoplasia by self-assessment for human papillomavirus DNA [research letter].** *Lancet* 354:1970 (December 4, 1999).
This study evaluated the sensitivity of HPV tests on self-collected specimens and compared it with the detection rate of specimens obtained from the cervix by gynecologists. A total of 247 patients attending a German colposcopy clinic self-introduced a cytobrush into the vagina for specimen collection and were examined by gynecologists who took Pap smears and an additional cytobrush specimen. Ninety-four percent of patients reported preferring the self-sampling to sampling by a physician. HPV positive results were found by 53 percent of the patients' samples compared to 42 percent by physician-collected specimens. Both test methods had a sensitivity of 93 percent for high-grade dysplasia and invasive cervical cancer. The authors concluded that self-sampling is a reliable method of testing for HPV and may be useful in settings in which cytology is not readily available, especially if these study findings can be reproduced in larger studies.

Jacobson, D. et al. **Concordance of human papillomavirus in the cervix and urine among inner city adolescents.** *Pediatric Infectious Disease Journal* 19(8):722–728 (August 2000).
A study of HPV in cervical samples and in urine found a high prevalence of HPV in both types of samples. Specimens from 80 sexually active adolescent women in Baltimore, Maryland, were tested for HPV DNA using both PCR and Probe B of Hybrid Capture. The presence of HPV was extremely high in the cervix (90%), and lower in the urine (75%). One adolescent tested positive for HPV in urine alone. Between the two sample sites, there was 82 percent agreement for presence of any type of HPV, and 40 percent agreement for specific HPV types. Despite the differences in sensitivity between the samples, the results indicate that HPV testing of urine samples could be useful outside of clinical situations. Urine testing can be useful in epidemiologic studies and in monitoring infected women, situations where obtaining genital specimens is difficult.

Johnston, C. **Quantitative tests for human papillomavirus.** *Lancet* 355:2179–2180 (June 24, 2000).
This commentary focuses on the relationship between infection with HPV DNA type 16, viral load, and risk of developing cervical cancer. Studies in this issue of the *Lancet* indicate that infection with a high viral load of HPV 16 many years prior to diagnosis of cervical cancer increases the risk of developing cancer, and those with persistently high viral loads are most at risk. These studies also suggest that cervical cancer is a slowly developing disease. Since HPV 16 has not been shown to be a useful predictor of cervical cancer risk by itself, except among those with a high viral load, is it a useful screening test? If viral load with HPV 16 is used to identify women at risk for high-grade disease, what should be done for these women now in the absence of any vaccine or treatment for HPV infection? The author concludes that thought needs to be given to whether these new viral tests offer substantial improvement over the Pap smear.

Josefsson, A. et al. **Viral load of human papilloma virus 16 as a determinant for development of cervical carcinoma in situ: a nested case-control study.** *Lancet* 355:2189–2193 (June 24, 2000).
This study investigated whether the amount of HPV DNA detected in cervical smears is a useful predictor of progression to cervical cancer in situ. Analysis of multiple smears from 478 women with cervical cancer (cases) and 608 matched controls showed that the risk of cervical cancer increased as the amount of HPV 16 DNA in the sample increased. The presence of high amounts of HPV 16 DNA is a major risk factor for developing cervical cancer. The positive predictive value of these results was too low to enable the test to be used as a single test for cancer risk except in women with the highest amounts of HPV DNA. However, the authors indicate that a quantitative test for HPV DNA has the potential to predict cancer risk at an earlier stage than current screening tools are able to do.

Kaufman, R.H. et al. **Relevance of human papillomavirus screening in management of cervical intraepithelial neoplasia.** *American Journal of Obstetrics and Gynecology* 176(1):87–92 (January 1997).
The goals of this study were to evaluate the utility of HPV-DNA testing in facilitating management decisions for women with abnormal Pap smears and to determine the prevalence of a positive HPV test result in these women. A total of 1,128 women who had abnormal Pap smears and were referred to a colposcopy clinic were evaluated in the clinic with a repeat Pap smear, HPV-DNA testing, and colposcopy. Of these, 172 (35.4%) of 486 women with low-grade lesions had high-risk HPV DNA detected; 263 (44.4%) of 592 women with high-grade lesions had high-risk DNA detected. High-risk DNA was detected in 38.7 percent of 527 and 56.2 percent of 267 women with biopsies showing CIN I and CIN II or III, respectively. The DNA test for detecting biopsy-confirmed CIN II or III had a sensitivity value of 55.7 percent; its positive predictive value was 34.9 percent. The results showed that HPV is causally associated with cervical cancer and that HPV-DNA testing does not appear to be a cost-effective measure in detecting high-grade CIN.

Koss, L. **Human papillomavirus testing as a screening tool for cervical cancer**. *JAMA* 283(19):2525–2526 (2000).
In this letter, the author questions the conclusions of Schiffman et al. 2000, that HPV testing of women older than age 35 is as effective or better than the Papanicolaou test in screening for cervical cancer. Koss argues that waiting until age 35 or 40 to test for high-risk HPV infection puts the lives of many younger women at risk. On the other hand, HPV testing of women ages 18 to 35, the ages at which most precancerous infection occur, would be misleading because of the high false positive rate of the test. Although the Pap test has a significant false-negative rate, the technique of testing for HPV is not mature enough to be its replacement, according to Koss. Schiffman and colleagues reply that HPV testing and Pap testing can be used to improve cervical cancer screening. At minimum, HPV-DNA testing can be recommended to standardize cytologic diagnoses in different laboratories.

Kuhn, L. et al. **Human papillomavirus DNA testing for cervical cancer screening in low-resource settings.** *Journal of the National Cancer Institute* 92(10):818–825 (May 17, 2000).
Given the many barriers to effective cytology screening in low-resource settings, this study evaluated HPV-DNA testing as an alternative. Cervical samples from 2,944 South African women ages 35 to 65 were tested for high-risk types of HPV using the Hybrid Capture I assay (HC-I). The screening included Pap smear, direct visual inspection of the cervix, and Cervicography (35 mm photograph of cervix). Women with any positive result were referred for colposcopy. Samples from a group of women with disease and from a random sample of disease-free women were retested for HPV DNA using the Hybrid Capture II assay (HC-II). Of the 86 women with high-grade squamous intraepithelial lesions (SILs) or invasive cancer, 73.3 percent were positive for a high risk type of HPV DNA using HC-I assay, and 88.4 percent were positive using the HC-II assay. HPV-DNA testing using the HC-II assay was more sensitive than cytology for detecting high-grade SILs and invasive cancer, and testing with the HC-I assay was equally sensitive. Cytology, on the other hand, had better specificity (96.8%) than either HC-I (87.8%) or HC-II (81.9%). By adjusting the test cut-off level, HPV-DNA testing can identify 57 percent of women with high-grade SIL or cancer, and limit the number of women with no cervical disease as HPV-DNA positive (false positives) to less than 5 percent. Given the equivalent or better sensitivity of HPV-DNA testing as compared to cytology, and because HPV-DNA testing may be easier to implement than cytology screening, HPV testing should be considered for primary cervical cancer screening in low-resource settings. Cost-effectiveness studies of HPV-DNA testing are needed to further evaluate its application.

Lytwyn, A. et al. **Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial.** *Canadian Medical Association Journal* 163(6):701–707 (September 19, 2000).
This Canadian study compared the accuracy of HPV-DNA testing with 6-month repeat Pap tests in detecting cervical intraepithelial neoplasia (CIN) II or III among women with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL). The authors found that HPV-DNA testing detected significantly more cases of CIN II or III than delayed

repeat Pap smears, but at greater cost. A cost-effectiveness analysis determined that the cost of HPV-DNA testing was Canadian $3,003 per additional case of CIN II or III detected. The authors conclude that HPV-DNA testing resulted in better detection and in fewer women lost to follow-up.

Manos, M.M. et al. **Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results.** *Journal of the American Medical Association* 281(17):1605–1610 (May 5, 1999).
This study, conducted in California, USA, compared a newer screening method with a more traditional method to determine whether women with atypical squamous cells of underdetermined significance (ASCUS) could be better served by the newer screening method. A total of 995 women with ASCUS Pap test results participated in the study. Under the new method, HPV-DNA testing was conducted on 995 ASCUS specimens, and those cases found to be HPV positive were referred directly to colposcopy. The authors found that the sensitivity of this method for detecting high-grade squamous intraepithelial lesions (HSILs) was equivalent to or greater than the traditional method of taking repeat Pap smears. In addition, because this screening method uses the same specimen for both cytology and HPV testing, it reduces the number of colposcopic examinations and follow-up visits (as well as patient anxiety and loss to follow-up). The authors believed the savings achieved by fewer visits and procedures would offset the cost of implementing the HPV-DNA testing.

Schiffman, M. et al. **Human papillomavirus DNA remains detectable longer than related cervical cytologic abnormalities.** *Journal of Infectious Diseases* 186:1169–1172 (2002).
HPV persistence is typically measured by using repeat HPV DNA tests or cervical cytological tests over time. To study the timing of HPV DNA clearance as it relates to the regression of cervical abnormalities, researchers assessed a sample of 840 women at six-month intervals for two years. Results showed that HPV DNA persists longer than cervical cytologic abnormalities. These results support the conclusion that women with negative HPV tests are at low risk of having undetected cervical lesions. They also indicate that HPV DNA testing may have a role in triage of women with ambiguous cytology results.

Schiffman, M. et al. **HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica**. *JAMA* 283(1):87–93 (January 5, 2000).
This study evaluated use of an HPV screening test to detect high-grade cervical lesions and cancer among more than 9,000 sexually active women age 18 and older in Guanacaste province, Costa Rica. In addition to HPV testing, women underwent conventional Pap smears and visual screening using cervicography. Samples also were prepared for ThinPrep cytologic analysis. The study found that HPV screening (using the Digene Hybrid Capture II test with a detection threshold of 1.0 pg/mL for 13 oncogenic HPV types) resulted in detection of 88.4 percent of high-grade cervical lesions and cancers, with a specificity of 89 percent. When results were calculated by age tertile (18 to 30, 31 to 40, and 41 and older), specificity was highest (94%) for older women. The percentage of lesions and cancers detected was lower (75%) for the original Hybrid Capture test (which has a detection threshold of 10pg/mL for 11 oncogenic types). Overall, HPV-DNA testing using the Hybrid Capture II test was more sensitive than conventional Pap testing (88.4 versus 77.7%) for detection of high-grade lesions and cancers, but less specific (89% versus 94%). The authors concluded that, while more data are needed on various factors that can affect the results of HPV testing (such as analytic cut offs and geographic variation in HPV types), the method clearly has "come of age" technically and should be increasingly useful in cervical factors screening efforts.

Walboomers, J.M.M. et al. **Human papillomavirus is a necessary cause of invasive cervical cancer worldwide.** *Journal of Pathology* 189(1):12–19 (September 1999).
In this study, researchers reexamined data from an earlier study (Bosch et al. 1995) that had confirmed a global association between HPV infection and cervical cancer by detecting HPV DNA in 93 percent of more than 1,000 cervical cancer specimens collected worldwide. The reexamination of data found many HPV-positive samples that had been false-negative in the previous study due to integration events affecting L1 sequences, a possibility that had been suggested by Bosch et al. By reanalyzing samples and excluding inadequate specimens, the current study found the worldwide HPV prevalence in cervical carcinoma to be 99.7 percent. This represents the highest percentage reported to date. The authors argue that the extreme rarity of HPV-negative cervical cancer reinforces the rationale for HPV testing in addition to, or perhaps even instead of, conventional screening methods.

Womack, S.D. et al. **HPV-based cervical cancer screening in a population at high risk for HIV infection.** *International Journal of Cancer* 85:206–210 (2000).
This study, involving 466 Zimbabwean women, evaluated the potential for using HPV testing to screen HIV-infected women for cervical dysplasia. Pap smears and samples for HIV and HPV testing (using Digene's HC II test) were obtained from all women. The study found that over half of the women tested were HIV-positive. HIV positivity was associated with a twofold increase in HPV prevalence and a threefold increase in HGSIL prevalence. The sensitivity and specificity of HPV-DNA testing for HGSIL were 91 percent (95% CI = 78–97%) and 41 percent (95% CI = 35–48%) for HIV-positive women; 62 (95% CI = 32–86%) and 75 percent (95% CI = 68–80%) for HIV-negative women. The negative predictive value for the test for each group was over 95 percent. The authors conclude that HPV-DNA testing is not an ideal test for HGSIL in HIV-positive women because of its relatively low specificity. At the same time, they noted that since HIV-positive women infected with HPV are at high risk of cervical disease, they should be provided with regular follow-up care. The authors also note that the ultimate usefulness of HPV-DNA testing as a screening test for cervical cancer must be decided based on local health priorities, policies, and capabilities.

Wright, T.C. et al. **HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer**. *Journal of the American Medical Association* 283(1):81–86 (January 5, 2000).
This study evaluated use of HPV screening tests (using self-collected and clinician-obtained samples) to detect high-grade cervical lesions and cancer among more than 1,400 previously unscreened black South African women aged 35 to 65. In addition to HPV testing, women underwent conventional Pap smears, STI testing, visual inspection of the cervix with acetic acid wash (magnified and unmagnified), and cervicography. The sensitivity of HPV-DNA testing (see Schiffman 2000 for more information about the Digene Hybrid Capture II test) of self-collected vaginal samples was 66.1 percent for detection of high-grade lesions and cancer; the false-positive rate was 17.1 percent. The sensitivity of HPV-DNA testing of clinician-collected samples was 83.9 percent; the false-positive rate was 15.5 percent. In comparison, the sensitivity of conventional Pap smear (with low-grade SIL and higher cytologic abnormality classified as positive) was 60.7 percent, with a false-positive rate of 3.2 percent. In summary, HPV-DNA testing using self-collected vaginal samples was less specific, but as sensitive as conventional Pap testing for detecting high-grade cervical disease in women age 35 or older (it is important to note that self-collection occurred at a clinic after specific instructions on how to obtain the sample). The authors concluded that HPV-DNA testing using self-collected vaginal samples holds promise for simplifying cervical cancer screening in many settings, although low specificity remains a problem. They discussed the need to assess two-stage screening protocols (for example, HPV testing followed by a Pap smear or visual inspection) to improve specificity.

Ylitalo, N. et al. **Consistent high viral load of human papillomavirus 16 and risk of cervical carcinoma in situ: a nested case-control study.** *Lancet* 355: 2194–2198 (June 24, 2000).
The authors sought to clarify the association between HPV 16 viral load and cervical cancer by analyzing multiple smears from 478 women with cervical cancer (cases) and 608 controls up to 26 years prior to diagnosis. The results showed that smears from the cases showed an increased viral load of HPV 16 thirteen years or more before diagnosis, often when the smear was cytologically normal. Women with high HPV 16 viral loads had a relative risk of cancer at least 30 times greater than women negative for HPV 16 more than a decade before diagnosis. Among women infected with a high viral load before age 25, about one-quarter developed cervical cancer within 15 years. Based on these findings, the authors conclude that quantitative HPV-DNA testing, in addition to cytological screening, could identify women at high risk of cervical cancer.

Top of page

The promise of HPV vaccines

Coursaget, P. and Muñoz, N. **Vaccination against infectious agents associated with human cancer.** *Cancer Surveys* 33:355–381 (1999).
Infectious agents account for about one-quarter of all cancer cases in the developing world, which creates enormous potential for vaccines. This article reviews the rationale for and current state of research on prophylactic and therapeutic vaccines against hepatitis B virus, human papillomavirus, and *Helicobacter pylori*. The authors conclude that many technical and practical problems remain before a safe, effective, inexpensive HPV vaccine can be produced for mass use, but that lessons learned from the introduction of the hepatitis B vaccine should expedite the process.

De Vuyst, H. et al. **Distribution of human papillomavirus in a family planning population in Nairobi, Kenya.** *Sexually Transmitted Diseases* 30(2):137–142 (February 2003).
HPV type prevalence has been reported to vary by region. This article reports results from a cross-sectional study of 429 women to determine the prevalence and distribution of HPV types among women attending a family planning clinic in Nairobi, Kenya. The mean age of the women was 35.2 years (standard deviation 6.5 years). A positive finding on biopsy or curettage was referred to as the reference test. Results showed 30 women (7.0%) with LSIL (CIN 1), 29 cases (6.8%) of HSIL (9 CIN 2 and 20 CIN 3), and one case (0.23%) of invasive cancer. Results of the HPV tests using PCR revealed 190 women (44.3%) were HPV positive. Among HPV positive samples, the most common HPV types were HPV 52 (17.9%), HPV 16 (14.7%), HPV 35 (11.6%), and HPV 66 (9%). Among women with HSIL, the most common HPV types were HPV 16 (35.7%), HPV 52 (25%), and HPV 35 (17.9%). As expected, strong associations were reported between having HSIL and being infected with a high-risk HPV type. The relative risk (RR) for HSIL was greatest for HPV 16 (RR=88.5). HPV 35 had a RR of HSIL of 54.3 and HPV 52 was associated with a RR of 49.2. In contrast to other studies, HPV 16 was not the most prevalent type and the authors conclude that the high prevalence of HPV 52 and 66 in this East African population warrants further research to tailor vaccines to take into account regional variations.

Duggan-Keen, M.F. et al. **Papillomavirus vaccines.** *Frontiers in Bioscience* 3:1192–1208 (1998). Available at: www.bioscience.org/1998/v3/d/duggan/d1208.htm).
Both prophylactic and therapeutic vaccines are a promising approach to fighting HPV, given the epidemiology of HPV-related disease, the life cycle of the virus, and natural immunity against HPV. This review article compares the mechanisms, advantages, and disadvantages of various candidate vaccines, including virus-like particles, proteins, peptides, viral vectors, DNA vaccines, bacterial

vectors, and dendritic cells. Assessing the efficacy of prophylactic vaccines raises the problem of choosing an appropriate study size and trial endpoint, and deciding how to measure significant antibodies and cytotoxic T-cells. Cost, ease of implementation, and stability are important considerations in developing a vaccine for widespread prophylactic use. Generating mucosal immunity poses a challenge, as does the genetic instability of tumors.

Galloway, D.A. **Is vaccination against human papillomavirus a possibility?** *Lancet* 351:22–24 (1998).
HPV potentially is amenable to vaccination because it is not prone to mutation and has just eight genes. Animal models suggest that both prophylactic and therapeutic vaccination is feasible. To make a substantial impact on the prevalence of cervical cancer, a prophylactic vaccine must be multivalent and must generate high titers of neutralizing antibodies at the mucosal surface. Goals for a therapeutic vaccine include eliminating residual cancer, the regression of existing disease, and preventing the progression of low–grade disease. The scientific basis for a therapeutic vaccine is weakened by two unresolved questions: Which antigen should be targeted? And what type of immune response mediates regression? Despite these and other challenges, the author concludes that the prospects for HPV vaccination are strong.

Goldie, S.J. et al. **A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine.** *International Journal of Cancer* 106:896–904 (2003).
This study utilizes a decision-analytic model to estimate the impact of a prophylactic HPV-16/18 vaccine on LSIL, HSIL, and HPV prevalence and the reduction of cervical cancer. The model simulated the age-specific prevalence of LSIL, HSIL, and cervical cancer for a cohort of 100,000 women immunized at age 13. The model also explored other assumptions about vaccine efficacy, coverage, and waning immunity. According to model projections, with 100 percent coverage, a vaccine that is 98 percent effective will produce an approximate 98 percent decrease in cancers related to HPV type 16/18 and a 51 percent reduction in total cancers. The lower percent reduction in total cancers (51%) takes into account competing risks from non-16/18 HPV associated cancers; women vaccinated against HPV type 16/18 could acquire an alternative high-risk type HPV that develops into cervical cancer. A vaccine with 75 percent effectiveness would result in a reduction of 70 to 83 percent of HPV-16/18 associated cancers. The model demonstrated how the impact of the HPV-16/18 vaccine varied with the proportion of the population vaccinated. When a vaccine with 98 percent efficacy covered only 50 percent of the population, the reduction in cervical cancer dropped to less than 30 percent. However, a partially effective vaccine (50 to 75 percent effective) that covers 75 percent of the population would be more effective than a highly effective vaccine with low coverage.

Kahn, J.A. et al. **Attitudes about human papillomavirus vaccine in young women.** *International Journal of STD & AIDS* 14(5):300–306 (May 2003).
This study explored young women's attitudes toward and intention to receive a human papillomavirus (HPV) vaccine if available. Fifty-two women between the ages of 18 and 30 years answered survey questions on vaccine acceptability. The majority of respondents knew that HPV was sexually transmitted and could be asymptomatic, that women with HPV may need more frequent Pap smears, and that an abnormal Pap smear may indicate HPV infection. Other knowledge questions received widely varied percentages of correct answers. Attitudes toward receiving the vaccine were positive for the majority, with 89 percent responding that it would be a good idea for themselves and for their daughters (81%). Receiving the vaccine did not appear to change women's risk behaviors, with the majority of respondents stating that it would not influence the number of sexual partners, use of condoms, or anxiety about smoking cigarettes. Several variables were statistically significantly associated with young women's intention to receive the vaccine, including knowledge level, personal beliefs about vaccination, beliefs that others would approve, and having a higher number of sexual partners.

Koutsky, L.A. et al. **A controlled trial of a human papillomavirus type 16 vaccine.** *New England Journal of Medicine* 347(21):1645–1651 (2002).
This article presents promising evidence of the effectiveness of a vaccine against HPV type 16, the most common HPV type linked to cancer. The authors conducted a randomized double-blinded trial of the effectiveness of the vaccine versus a placebo in 2,392 women with no history of prior abnormal cytology findings. Primary analysis was conducted on 1,533 of the women after a median of 17.4 months of follow-up. At follow-up, the vaccine was 100 percent effective: none of the women who received the vaccine developed persistent HPV 16 infection, precancerous cervical lesions, or cancerous growth. In contrast, 41 women who received the placebo developed persistent HPV 16 infection, with 9 of the 41 developing precancerous lesions. HPV 16 is responsible for about half of all cervical cancers; however, the authors caution that a vaccine that prevents more than one type of HPV may be "more advantageous." Researchers also caution that the long-term efficacy of the vaccine is currently unknown.

Lowy, D.R. and Schiller, J.T. **Papillomaviruses: prophylactic vaccine prospects**. *Biochimica et Biophysica Acta* 1423: M1–M8 (1998).
This article concentrates on one type of potential prophylactic HPV vaccine: virus-like particles. The molecular structure and immunogenicity of viral capsids make virus-like particles a strong candidate vaccine. Studies in dogs, rabbits, and cows confirm that these particles protect against challenge with papillomavirus, probably by inducing neutralizing antibodies. However, it is not yet certain whether systemic immunization with virus-like particles will confer protection against genital mucosal HPV infections in humans. This may require a different vaccine protocol. Alternatively, nonstructural proteins might be added to increase their effectiveness as vaccines; these chimeric virus-like particles might be able to eliminate early cervical lesions that escaped neutralization.

Top of page

Cervical Cancer Prevention

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Annotated Bibliography

This is **page 2** of the Cervical Cancer Prevention Annotated Bibliography. This page contains:

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Primary prevention of cervical cancer

Castellsague, X. et al. **Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners.** *New England Journal of Medicine* 346(15):1105–1112 (2002).
Data from a large multi-center case-control study were pooled to assess whether male circumcision was related to reduced risks of penile human papillomavirus (HPV) and thus subsequent cervical cancer in female partners. Circumcision status was self-reported and HPV status determined by PCR. Authors adjusted for potential confounders that included age at first intercourse and number of sexual partners. Results showed circumcised men had a reduced risk of having HPV infection as compared to uncircumcised men (odds ratio, .37; 95 percent confidence interval, .16 to.85). The study then analyzed the risk of cervical cancer among monogamous women whose husbands had six or more sexual partners and found a reduced risk of cervical cancer among women whose husbands were circumcised (adjusted odds ratio, .42; 95 percent confidence interval, .23 to .79).

Coker, A.L. et al. **Barrier methods of contraception and cervical intraepithelial neoplasia.** *Contraception* 45(1):1–10 (1992).
The goal of this U.S. case-control study of 103 cases with biopsy-confirmed, high-grade dysplasia and 258 controls with normal cervical cytology was to examine risk factors for cervical intraepithelial neoplasia (CIN). Study participants were interviewed about their sexual and reproductive history, Pap smear screening, cigarette exposures, and contraceptive use patterns. After adjusting for confounding factors, the authors found that cases were half as likely as controls to ever have used a barrier method (defined as condom, spermicide, or diaphragm) (OR = 0.5; 95% CI = 0.2–0.9). When analyzed separately, condom (OR = 0.5; 95% CI = 0.2–1.0) and diaphragm use (OR = 0.3; 95% CI = 0.1–0.9) both were associated with a decrease in risk, while spermicide use was not.

Grimes, D.A. and Economy, K.E. **Primary prevention of gynecologic cancers.** *American Journal of Obstetrics and Gynecology* 172:227–235 (1995).
This review article examines the epidemiologic characteristics of cervical, endometrial, and ovarian cancers as they relate to primary prevention strategies. The review was limited to invasive cancers. Regarding cervical cancer, the authors concluded that avoiding cigarette smoking may protect against cervical cancer and a diet rich in vitamin C may reduce the risk of cervical cancer. They also determined that the long-term use of oral contraceptives was associated with cervical cancer, but noted the difficulty in controlling for the potential effects of cigarette smoking, sexual history, and the frequency of Pap smear screening. The authors also concluded that the use of barrier methods of contraception (studies included diaphragm, condoms, foam, spermicides, and contraceptive jelly) protects against invasive cervical cancer. Finally they noted that since early age at first intercourse, the frequency of intercourse at an early age, and high numbers of sexual partners are all associated with cervical cancer, abstinence and delaying of first intercourse should decrease the risk of cervical cancer.

Hildesheim, A. et al. **Barrier and spermicidal contraceptive methods and risk of invasive cervical cancer.** *Epidemiology* 1:226–272 (1990).
The goal of this U.S. case-control study of 479 invasive cervical cancer cases and 788 controls was to examine the effects of barrier and spermicidal methods of contraception on cervical cancer risk. Study participants were interviewed about contraceptive practices as well as other factors that might affect cervical cancer risk, including reproductive history, sexual behavior, Pap smear screening history, and smoking. After adjusting for confounding factors, the authors found no significant association with condom, diaphragm, or vaginal spermicide use. They noted a slight but nonsignificant decrease of cervical cancer with long-term (more than 5 years) diaphragm use (OR = 0.8; 95% CI = 0.4 1.6).

Koutsky, L.A. and Kiviat, N.B. **Genital human papillomavirus.** In: *Sexually Transmitted Diseases.* 3rd ed. Holmes, K. K. et al., eds. New York: McGraw-Hill (1999).
This chapter provides a detailed overview of the issues related to genital human papillomavirus, including the definition, prevalence and incidence, geographic distribution, transmission, risk factors, clinical manifestations, management, and prevention.

Mindel, A. and Tideman, R. **HPV transmission—still feeling the way [commentary]**. *Lancet* 354:2098–2099 (December 18–25, 1999).
This commentary critically discusses findings by Sonnex et al. that showed a potential for transmission of HPV infection by finger-genital contact. The authors state that finger-genital transmission of HPV is possible, but that transmission would rely on a sequence of events highly unlikely to occur. They note that detection of HPV DNA on fingertips does not necessarily imply the presence of intact, infectious virus. They also note that HPV transmission would require actual finger transfer of a sufficient quantity of live virus and a corresponding breach of genital skin. They conclude the article by stating that finger-genital contact usually is accompanied by genital-to-genital contact, where transmission is far more likely to occur. They recommend condom use as the only intervention currently proven to reduce the risk of HPV transmission.

Sawaya, G.F. et al. **Frequency of cervical smear abnormalities within 3 years of normal cytology.** *Obstetrics and Gynecology* 96(2):219–223 (August 2000).
This U.S. study compared cervical screening outcomes at one, two, and three years after screening. While annual Pap

smear screening has contributed significantly to a decline in the U.S. mortality rate from cervical cancer, it is less clear whether women in the United States with normal smears need annual follow-up or could be screened less frequently. This study sought to determine the incidence of abnormal smears after normal smears, and to see how rates vary by age and time since the last normal smear. The study analyzed 128,805 women with normal baseline smears and follow-up smears 9 to 36 months later. The study found that women screened within three years of a normal smear all had the same risk of developing high-grade squamous intraepithelial lesion (SIL) or worse, but such results were uncommon. Women under age 30 were more likely to have a low-grade abnormal smear, and the incidence declined with age. The authors concluded that the best screening protocols for women with recent normal Pap smears should be based on comprehensive modeling studies that incorporate the true risks and benefits of repetitive screening.

Sellors, J.W. et al. **Comparison of self-collected vaginal, vulvar, and urine samples with physician-collected cervical samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions.** *Canadian Medical Association Journal* 163(5):513–518 (September 5, 2000).
In this study, 200 women referred to a colposcopy clinic at a teaching hospital in Ontario, Canada, provided self-collected vulvar, vaginal, and urine samples for HPV testing. A physician also collected cervical samples for testing, and the respective test results were compared. Positive HPV test results obtained on vaginal swabs by the women themselves had a 86.2 percent sensitivity for high-grade squamous intraepithelial lesions (HSIL, equivalent to CIN grade II or III), while the cervical samples obtained by the physician showed a sensitivity of 98.3 percent. The sensitivity of self-collected vulvar and urine samples were 62.1 percent and 44.8 percent respectively. The study found the self-sampling methods to be generally acceptable to the women. Given that Pap smear accuracy is far from perfect and that cytology programs are not feasible in many developing countries, the authors conclude by recommending further evaluation of HPV testing using self-collected samples, especially in areas where cytological screening services are limited.

Sellors, J.W., Mahony, J.B., et al. **Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada.** *Canadian Medical Association Journal* 163(5):503–508 (September 5, 2000).
This study of 955 Canadian women ages 15 to 49 was undertaken to increase understanding of the natural history of HPV infection. HPV testing showed that women age 20 to 24 years had the highest prevalence of HPV infection at 24 percent. Prevalence dropped with increasing age, to a low of 3.4 percent in women 45 to 49 years old. The risk factors for HPV infection identified in this study are never-married, divorced, or separated status; more than three lifetime sexual partners; more than one partner in the previous year; cigarette smoking; and current use of oral contraceptives. As other studies have found, there also was a strong association between HPV and abnormal cytological results. The authors call for more HPV survey studies to be done in countries with various rates of cervical cancer in order to better assess risk factors, clearance rates, and acquisition of different types of infection over time.

Shepherd, J. et al. **Interventions for encouraging sexual lifestyles and behaviours intended to prevent cervical cancer** (Cochrane Review). In: *The Cochrane Library,* Issue 3, 1999. Oxford: Update Software. [See RHO's WHO RHL page for more information.]
This meta-analysis reviews the effectiveness of health education in promoting sexual risk reduction among women in order to reduce transmission of human papillomavirus (HPV). The review included ten studies of education programs, all of which had the primary aim of preventing HIV and other STIs rather than cervical cancer. The review found that educational interventions targeting socially and economically disadvantaged women in which information provision is complemented by sexual negotiation skill development can encourage at least short-term sexual risk reduction behavior. This has the potential to reduce the transmission of HPV and, as a result, the incidence of cervical cancer.

Sonnex, C. et al. **Detection of human papillomavirus DNA on the fingers of patients with genital warts.** *Sexually Transmitted Infections* 75(5):317–319 (October 1999).
This study, which detected HPV DNA on the fingers of patients with genital warts, raises the possibility that HPV infection can be transmitted through finger-genital contact. The authors took samples from genital lesions and fingertips of 14 men and 8 women who had genital warts. From the genital samples, they detected HPV DNA in all 8 female samples and 13 of 14 male samples. In a separate testing of samples taken from fingertips of the same subjects, they detected HPV DNA in 3 women and 9 men. The authors further determined that the same type of HPV DNA was present in the genital and finger samples of one woman and five men. Although sexual intercourse is considered to be the usual

mode of transmission for genital HPV infection, this study shows that some patients with genital warts carry HPV of the same type on their fingers. This points to a potential for transmission of HPV infection by finger-genital contact.

Thomas, D.B. et al. **Human papillomaviruses and cervical cancer in Bangkok. The role of husbands and commercial sex workers**. *American Journal of Epidemiology* 153(8):740–748 (2001).
This article in is the third in a series of three studies on cervical cancer in Bangkok. The results highlights the potential for men to play a role in increasing their wives risk of HPV infection and cervical cancer. According to the findings, women whose husbands report frequent contact with sex workers (280 or more visits over their lifetime) were more than three times as likely to develop invasive cancer than women whose husbands reported no contact with sex workers. The women in the study reported their husband was their only sexual partner throughout their lifetime, leading to the conclusion that their husbands may be acquiring high-risk HPV infection from contact with sex workers and transmitting it to their wives.

Wen, L.M. et al. **Risk factors for the acquisition of genital warts: are condoms protective?** *Sexually Transmitted Infections* 75(5):312–316 (1999).
This study, conducted at Australia's largest STI clinic, included 977 patients with genital warts and 977 controls matched by sex and date of clinic attendance. The study goals were to determine risk factors for acquiring genital warts and to determine whether condoms offer protection against infection. Independent risk factors for genital warts were found to be younger age, greater number of lifetime sexual partners (primarily true for men), and smoking (men only). The authors noted that, although previous studies have failed to show a protective effect of condom use, this study found that consistent condom use significantly reduced the risk for both sexes of acquiring genital warts.

World Health Organization (WHO). ***Primary Prevention of Cervical Cancer.*** CAN/85.1. Geneva: WHO (October 3–November 2, 1985).
A WHO consulting group met in 1985 to consider possible approaches for primary prevention of cervical cancer. Given that cervical cancer is strongly linked to early onset of sexual activity and multiple sexual partners, the WHO group recommended sex education and studies in sexual behavior, while acknowledging that behavior is difficult to change. They recommended that development of vaccines for HPV be made a high priority, together with further study of the possible contribution of smoking to cervical cancer. They noted that there is no evidence to suggest a protective effect from hygiene, male circumcision, or nutrition, and that data are inconclusive on the role of oral or injectable contraceptives. They recommended that use of barrier methods, particularly condoms, should be encouraged.

Top of page

Screening: assessment of alternative approaches

Adab P, McGhee SM, Yanova J, et al. **Effectiveness and efficiency of opportunistic cervical cancer screening: comparison with organized screening.** *Medical Care.* 2004;42(6):600–609.
The authors developed a model to assess the effectiveness (percent reduction in incidence) and efficiency (number of smears per case prevented) of opportunistic screening compared to organized screening for cervical cancer prevention. Data on screening history were gathered from a cross-sectional study of 1,826 women aged 20 to 77 years, living in Hong Kong. Authors developed two models based on screening intervals. In the “optimistic” model, they assumed that women with two previous cytology screenings would return for their next screening at the same duration as their last smear. In the “pessimistic” model it was assumed that the interval for the women’s next screening would be 10 years or more. Based on these models, the reduction in incident cases of cervical cancer was between 26 percent (pessimistic model) and 31 percent (optimistic model) with 2,723 and 2,786 screening smears per cancer case prevented, respectively. Authors discussed the benefits of an organized screening program. Effectiveness typically increases with increased coverage of the population, resulting in a reduction of cervical cancer incidence. In their models, increased coverage did not affect efficiency. Reducing the screening interval also results in increased effectiveness but reduced efficiency. The authors concluded that the current Hong Kong screening system is less effective and efficient compared to an organized screening system that could achieve 80 percent coverage at 10-year intervals (effectiveness estimates were based on

models in a study produced by the International Agency for Research on Cancer [IARC], 1986).

Basu, P.S. et al. **Visual inspection with acetic acid and cytology in the early detection of cerivcal neoplasia in Kolkata, India.** *International Journal of Gynecological Cancer* 13:626–632 (2003).
This study analyzes the test characteristics of VIA, VIAM and cytology used for cervical cancer screening in Kolkata (Calcutta), India. A total of 5,881 women were screened using VIA, VIAM, and conventional cytology. True positive disease was defined as CIN 2 or 3 or carcinoma in situ. All women had colposcopic evaluation and biopsies were performed if indicated (1052, 17.9%) to determine final diagnosis. Thus, direct estimation of sensitivities, specificities, and predictive values was possible without the risk of verification bias. More women tested positive with VIA and VIAM than with cytology (18.7% and 17.7% compared to 8.2%). The sensitivity of VIA, VIAM and cytology was 55.7%, 60.7%, and 29.5%, respectively. The specificity of VIA, VIAM and cytology was 82.1%, 83.2%, and 92.3%, respectively. The improvement in sensitivity of VIAM over VIA, although small, was statistically significant ($P<0.01$), with no reduction or improvement in specificity. The sensitivities of VIA and VIAM are lower in this study than previously reported in other studies, and the authors comment that the use of nonmedical workers as compared to nursing or paramedical professionals may account for some of this difference.

Basu, P. et al. **Evaluation of downstaging in the detection of cervical neoplasia in Kolkata, India.** *International Journal of Cancer* 100:92–96 (2002).
This study sought to determine the sensitivity and specificity of downstaging (examining the cervix with the naked eye, also known as "unaided visual inspection") when used to detect cervical lesions. Downstaging was used to screen 6,399 women in Kolkata, India. Direct estimates for sensitivity and specificity were made after colposcopy was performed on all women and biopsies were taken for abnormal lesions. Using a low-threshold to detect high-grade lesions, downstaging had a sensitivity of 48.9 percent and a specificity of 75.8 percent. With a high-threshold downstaging, the sensitivity for detecting high-grade lesions was 31.9 percent and the specificity was 93.3 percent. The low sensitivity, and relatively low specificity when using the low-threshold test, means that large numbers of women would be falsely identified as having cervical neoplasia. On the other hand, the low specificity of the high-threshold test means that the test would miss a large proportion of women with disease. Authors conclude that downstaging is an inadequate test for primary screening for cervical neoplasia.

Belinson, J.L. et al. **Cervical cancer screening by simple visual inspection after acetic acid.** *Obstetrics and Gynecology* 98(3):441–444 (September 2001).
This study reports the sensitivity and specificity of using visual inspection with acetic acid (VIA) to screen 1,997 women between the ages of 35 to 45 years in rural Shanxi Province, China. VIA, colposcopy and directed biopsies were performed on all women. Sensitivity of VIA in this setting was equal to or greater than rates reported for conventional cytology. VIA had a sensitivity of 71 percent (61 of 86, 95% CI 60%, 80%) for detecting CIN II and higher and a specificity of 74 percent (1,420 of 1,911, 95% CI 72%, 76%) for detecting CIN II and higher. These results are comparable to the sensitivity and specificity reported in the University of Zimbabwe/Johns Hopkins University study. VIA's specificity for detecting CIN II lesions or higher was similar to specificity rates for colposcopy. Both VIA and colposcopy performed less well on smaller lesions that only appeared in one quadrant. The authors discuss several variables that could affect the performance of VIA, and comment that a region's available resources (human and financial) will help determine what screening tests are appropriate. They conclude that the low-cost, ease of training and implementation, and low infrastructure requirements for point-of-care diagnosis and treatment algorithm make VIA an attractive choice for cervical cancer screening in low-resource settings.

Blumenthal, P.D. et al. **Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear.** *International Journal of Gynecology & Obstetrics* 72:47–53 (2001).
The objective of this study was to examine whether performing combinations of visual inspection with acetic acid (VIA), HPV testing, and cytology would improve the specificity of VIA without decreasing its sensitivity. Data from a cervical cancer screening study conducted in Zimbabwe were analyzed using standard calculations of net sensitivity and specificity for the various combinations of the screening tests. Net sensitivity and specificity for VIA combined with HPV was calculated as 63.6 and 81.9 percent, respectively. The combination of VIA followed by HPV was more effective at detecting women with cervical disease than either Pap smear followed by HPV or HPV followed by Pap

smear. Combining VIA in sequence with another test also produced fewer false positives than using VIA alone. The authors comment that using VIA as the first test in a sequence has the benefit of immediate results, making it possible to perform a second test in the same visit, an important consideration in developing country settings. It is not possible, however, to have the immediate results from using either HPV or Pap smear as a second test. The authors conclude that making management decisions based on VIA alone, in settings where there is considerable loss to follow-up when women need to return for a second clinic visit, merits serious consideration.

Chirenje, Z.M. et al. **Situation analysis for cervical cancer diagnosis and treatment in East, Central and Southern African countries.** *Bulletin of the World Health Organization* 79(2):127–132 (2001).
This study collected interview and questionnaire data from randomly selected primary health care centers, district hospitals, provincial and tertiary hospitals in Kenya, Lesotho, Uganda, United Republic of Tanzania, and Zimbabwe during an eight-month period of 1997. The results revealed that although most countries had a basic infrastructure to support Pap smear screening, coverage was extremely low in all countries and women frequently presented with advanced-stage disease. Frequently cited reasons for the low screening coverage included a lack of policy guidelines on cervical cancer screening, an inconsistent stock of materials, and an inadequate number of trained cytotechnicians. Only 42 percent of district and provincial hospitals had treatment facilities for cone biopsies, but only 31 percent of provincial hospitals actually performed the procedure. Cryotherapy, a relatively inexpensive, reliable, and simple procedure, was only available in 4 percent of hospitals and health centers. These results highlight the great need for increased cervical cancer screening efforts in the region.

Coppleson, M. et al. **An electronic approach to the detection of precancer and cancer of the uterine cervix: a preliminary evaluation of Polarprobe.** *International Journal of Gynecological Cancer* 4:79–83 (1994).
This article describes preliminary results of an electronic device for detection of cervical cancer and its precursors, known as the Polarprobe. The Polarprobe is a computerized diagnostic instrument consisting of a pen-sized probe that is inserted into the vagina and moved across the cervix. The probe is attached to a portable computer that processes electrical and optical properties of cervical tissue and compares the information with data from normal or abnormal tissue. The study established recognition algorithms from analysis of results of 106 volunteers and then tested 77 additional volunteers. When comparing Polarprobe diagnosis with concurrently obtained histologic-colposcopic diagnosis, concordance between the two was 85 percent for low-grade intraepithelial abnormalities, 90 percent for high-grade abnormalities, and 99 percent for cancer.

Cullins, V. et al. **Cervical cancer prevention using visual screening methods.** *Reproductive Health Matters* 7(14):134–143 (1999).
Among the range of screening techniques being studied for use in low-resource settings, direct visual inspection (DVI)—also referred to as visual inspection with acetic acid (VIA)—is thought to have good potential for screening and treatment in one visit. However, the authors say caution is needed when applying a new approach in a mass screening program. DVI appears to have the same sensitivity but lower specificity than Pap smears, and could lead to overtreatment of many women who do not have disease. The standard forms of treatment (cryosurgery, laser ablation, or loop electrosurgical excision) all result in an open cervical ulcer that takes three to four weeks to heal. Prior to widespread screening using DVI studies need to determine (1) the complication rate of treatment when performed by mid-level clinicians; (2) the co-morbidity of treatment in a population where STIs and HIV are endemic; and (3) the acceptability of a screening program in which up to one-third of women will be unnecessarily treated. The relative risks and benefits of widespread DVI screening need to be carefully evaluated.

Denny, L. et al. **Two-stage cervical cancer screening: An alternative for resource-poor settings**. *American Journal of Obstetrics and Gynecology* 183 (2):383–388 (2000).
By using two screening tests sequentially to screen for cervical cancer, this study sought to reduce unnecessary treatment. A total of 1,423 women from Cape Town, South Africa, were screened using direct visual inspection with acetic acid with and without magnification, HPV DNA testing, cytological testing, and cervicography. Any woman with an abnormality on any test was referred for colposcopy. When used alone these tests respectively identified 24, 26, 23, and 23 cases of high-grade squamous intraepithelial lesion or cancer per 1,000 women. The respective tests would also classify 182, 71, 137, and 112 women without disease as having an abnormal result (false positives). When direct visual

inspection was used first, and only women with an abnormal result screened with HPV DNA testing, cytological testing, or cervicography, the number of cases identified dropped to 18, 16, and 18 per 1,000 women, respectively (lower sensitivity). However, the number of false positives also dropped significantly (greater specificity). Different settings would favor the use of different combinations of screening tests, but the two-stage approach offers an alternative to screening for cervical cancer in the absence of colposcopy.

Gaffikin, L. et al. **Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project.** *Lancet* 361:814-820 (March 8, 2003). [Erratum published in the *Lancet* 361 (9373):1994 (June 7, 2003).]
This article assesses an innovative approach to cervical cancer prevention in a rural community in Thailand. 12 nurses were trained to test women for cervical lesions using visual inspection with acetic acid (VIA). Women who tested positive after VIA were counseled by the nurses and offered treatment with cryotherapy. Overall 5999 women were tested with VIA. 798 women tested positive (VIA test-positive rate, 13.3 percent) and of those 618 were eligible for immediate treatment with cryotherapy. 609 of the 618 accepted immediate treatment. A total of 756 women received cryotherapy (either immediate or postponed). Women were counseled about potential side effects and complications and were instructed to return if any symptoms developed that could indicate a potential complication. Follow-up visits were scheduled for 3 months and 1 year post-treatment. 629 women returned for their first scheduled follow-up visit. Overall the majority of women were highly satisfied with the VIA and cryotherapy treatment and few complications arose. There were no major complications (admission, transfusion, or major surgery) needed as a result of the treatment. Unscheduled visits were made by 33 (4.4 percent) of the 756 women, and among those 33 women 17 needed a conservative outpatient procedure (2.2 percent of the total treated). Authors conclude that a VIA + cryotherapy single-visit approach is safe, effective, and feasible for programs in developing countries.

Gaffikin, L. et al. **Performance of visual inspection with acetic acid for cervical cancer screening: a qualitative summary of evidence to date.** *Obstetrical and Gynecological Survey* 58(8):543–550 (2003).
This article provides a qualitative summary of the key findings from original research studies on visual inspection with acetic acid (VIA). Authors conducted a systematic review of the literature using a PubMed search to identify relevant journal articles from 1982 through 2002. Overall, 16 articles were eligible for review. In seven of the 16 studies, data were available that allowed for the calculation of sensitivity and specificity of VIA. Based on the data from these seven studies, the authors present ranges, unweighted, and weighted averages (weighted averages based on the number of participants in the study) for the sensitivity and specificity. For VIA's sensitivity the range was from 66 to 96 percent; unweighted average, 82 percent; weighted average, 81 percent. For VIA's specificity the range was from 64 to 98 percent; unweighted average, 82 percent; weighted average, 83 percent. Overall these results reflect VIA performance when used to screen over 34,000 women in general health care settings in both developed and developing countries. Authors conclude that these data demonstrate that VIA's performance is similar to, and possibly superior to, cytology in identifying women with CIN when used in the same setting. More evidence is needed, however, on the long-term programmatic effectiveness in reducing cervical cancer.

Lazcano-Ponce, E.C. et al. **Cervical cancer screening in developing countries: why is it ineffective? The case of Mexico.** *Archives of Medical Research* 30:240–250 (1999).
This evaluation of the Mexican national cervical screening program seeks to explain why the program (established in 1974) has failed to decrease cervical cancer mortality in Mexico. They authors found that the low effectiveness of screening is due primarily to issues surrounding Pap smear quality and coverage. Pap quality is low: 64 percent of a random sample of specimens lacked endocervical cells, and false-negative indices from reading centers ranged between 10 and 54 percent. The authors also found that women tend to seek screening only after they are symptomatic, rather than as a preventative measure. Pap smear coverage is particularly low in rural areas (30 percent compared to 64 percent of women age 15–49 in Mexico City). Qualitative research has highlighted additional difficulties, including a preference for female providers and a perception that public services are impersonal and lack necessary privacy. In rural areas, the authors found the perception of cancer and death to be synonymous; they also found that women were reluctant to risk disapproval from their sexual partners by seeking testing. The authors offer a proposal to reorganize Mexico's screening program through five main strategies: (1) increased coverage; (2) improved quality control of how cervical smears are taken; (3) better interpretation of Pap tests; (4) guaranteed treatment for those whose tests show abnormalities; and (5) improved follow-up.

Mandelblatt, J.S. et al. **Costs and benefits of different strategies to screen for cervical cancer in less-developed countries.** *Journal of the National Cancer Institute* 94(19):1469–1481 (October 2, 2002).
This study examines the costs and benefits of screening strategies used in cervical cancer prevention in less-developed countries. Using data from Thailand and a population-based model, the study evaluated the costs and benefits of seven strategies including visual inspection with acetic acid (VIA), Pap smear, and human papillomavirus (HPV) testing alone and in combination with other techniques. Compared with no screening (or screening programs that are not well organized), all strategies showed a reduction in mortality from cervical cancer, although the life years saved (LYS) and costs varied considerably. When the authors compared each strategy with the next less costly strategy, they found the least expensive option was screening with VIA, in five-year intervals. This strategy cost $517 per LYS and saved the greatest number of lives. Other strategies had reasonable cost-benefit results depending on maintaining high levels of follow-up. For example, if Pap smear sensitivity reached 80 percent and if 90 percent of women were seen for follow-up, then Pap smear may be a reasonable alternative. The authors emphasize the usefulness of cost-effectiveness data such as these to inform decision-making around health policies.

Megevand, E. et al. **Acetic acid visualization of the cervix: an alternative to cytologic screening.** *Obstetrics & Gynecology* 88(3):383–386 (September 1996).
This prospective study of 2,426 women in a squatter area in Cape Town, South Africa, investigated the value of visual inspection of the cervix using acetic acid as an alternative to cytologic screening. All women with a positive visual inspection screening or a positive cytology were referred for colposcopy and biopsy. Histology was obtained on all women with positive results on either test. The authors reported that 76 women had positive visual inspection results; of these, subsequent smears revealed squamous intraepithelial lesions (SIL) in 61 and no evidence of SIL in 15. The remaining 2,350 women had negative visual inspection results. Of these, however, 254 had positive cervical smears; only 11 of these had high-grade SIL on histology-confirmed cytology. Visual screening detected 20 of the 31 women (64%) who had high-grade SIL on both cytology and histology. The authors concluded that in situations where cytology-based screening for precancerous lesions is not available, visual inspection with acetic acid warrants consideration as an alternative screening method.

Meijer, C.J.L.M. et al. **Screening for cervical cancer: should we test for infection with high-risk HPV? [commentary]** *Canadian Medical Association Journal* 163(5):535–538 (September 5, 2000).
The authors comment on two Canadian studies by Sellors et al., and summarize the relationship between high-risk human papillomavirus (HPV) infection and the development of cervical cancer. Persistent infection with high-risk HPV can lead to cervical intraepithelial neoplasia (CIN), which then progresses to more severe CIN infection in some women, and to invasive cervical cancer in a subset of these women. The average period from initial infection with HPV to invasive cancer is estimated at 15 years. Infection with high-risk HPV is associated with increased sexual activity and changing sexual partners. However, because of the presence of transient infection in younger women, the authors suggest that women 30 years or older be screened with a test for high-risk HPV instead of or, in some cases, in addition to the Pap test. While not as effective as cytological screening, self-screening for HPV may be appropriate for women who do not participate in routine screening programs. The authors suggest that a "once-in-a-lifetime" HPV screen of 35-year-old women using self-collected samples could reduce cervical cancer in developing countries.

Murthy, N.S. et al. **Estimation of reduction in life-time risk of cervical cancer through one life-time screening.** *Neoplasma* 40(4):255–258 (1993).
Given the recommendation by the World Health Organization (WHO) in 1986 that countries with limited resources should aim to screen every woman once in her lifetime, this study attempted to determine at what age that screening could cause the greatest overall reduction in mortality from cervical cancer. The study, using data from three cities in India, compared rates of cervical cancer incidence in unscreened women with incidence in women screened once in their lifetime at different ages (between ages 20 and 64). The authors found that screening at age 45 would be most effective, factoring in the number of cervical cancer cases prevented and the number of productive years of life saved.

Nene, B.M. et al. **Early detection of cervical cancer by visual inspection: a population-based study in rural India.** *International Journal of Cancer* 68:770–773 (1996).

The goal of this study was to evaluate the use of unaided visual inspection by trained paramedical workers (PW) in detecting cervical cancer in poor-resource settings. Two PWs examined 1,954 women from the Maharashtra State, India, who were then seen by a gynecologist. PWs scored 1,120 (57.3%) and 118 (6%) women as having abnormal cervices using the low- and high-threshold criteria respectively, similar to the scores obtained by the gynecologist (1,162 and 113 respectively). The sensitivity values of visual inspection to detect cervical cancer by PWs using the low- and high-threshold criteria were 90 percent and 60 percent respectively; specificity values were 42.8 percent and 94.2 percent respectively. Similar values of sensitivity and specificity were also observed by the gynecologist. The authors concluded that unaided visual inspection probably is not a useful procedure for cervical cancer control. The cost savings achieved by 40 to 50 percent of visually normal women not requiring cytology examinations will be offset by those needing repeat examinations, colposcopy, and biopsy.

Ottaviano, M. and La Torre, P. **Examination of the cervix with the naked eye using acetic acid test.** *American Journal of Obstetrics & Gynecology* 143:139–142 (1982).
This study of 2,400 patients between the ages of 18 and 65 in Florence, Italy, evaluated the use of visual inspection and colposcopy before and after the application of acetic acid and compared the results of the two techniques. Before the application of acetic acid, they found that no clinical diagnosis, except overt carcinoma, was possible either with visual inspection or with the colposcope. In the comparison between "naked-eye" visual inspection with acetic acid (VIA) and colposcopy with acetic acid, VIA identified 307 of 312 women (98.4%) colposcopically assessed as having an atypical transformation zone. VIA also identified 1,568 of 1,584 (98.9%) of cases where colposcopy identified the cervix as normal. The authors concluded that the detection of precancerous cervical lesions should not depend on the possession of a colposcope.

Pengsaa, P. et al. **A self-administered device for cervical cancer screening in northeast Thailand.** *Acta Cytologica* 41 (3):749–754 (May 1997).
The goals of this study were to compare results of screening through a self-scraping device against a routine scraping method and to evaluate the acceptance of this new device among a group of rural women from Northeast Thailand. A total of 552 women participated in the study. The women were trained to use the self-scraping device and were reexamined by a gynecologist using the routine scraping method one week later. In both cases, the specimens were stained as Pap smears. The self-scraping method detected 13 abnormal Pap readings, 11 of which were confirmed by physician examination. No false negative readings were found, but the self-scraping method was not as accurate as physician examination for detection of inflammation. Responses to questionnaires about the device showed general acceptance among the women. The authors concluded that in areas where trained medical personnel are not available to carry out regular tests, the self-scraping method can be a useful screening tool.

Richart, R. **Screening: the next century.** *Cancer* 76:1919–1927 (November 15, 1995).
This article provides a comprehensive overview of existing and potential screening methods for application in both developing and developed countries. In addition to Pap smears, technologies reviewed for developing countries include unaided visual inspection with and without acetic acid (downstaging), aided visual inspection, and cervicography. Automated Pap machines and HPV DNA tests also are reviewed in the context of both high- and low-resource settings. The author addresses the effectiveness of various screening options as well as the likelihood that they will be available and cost-effective in high- and low-resource settings.

Sankaranarayanan R, Basu P, Wesley RS, et al. **Accuracy of visual screening for cervical neoplasia: results from an IARC multi-centre study in India and Africa.** *International Journal of Cancer.* 2004;110:907–913.
This article reports results from 11 cross-sectional studies of cervical cancer screening of 54,981 women in nine centers in Africa and India through the International Agency for Research on Cancer (IARC). Study participants were women aged 25 to 65. All women received VIA, VILI, and colposcopy, with biopsy if indicated. Female health workers trained in the testing procedures performed VIA and VILI. Medical staff performed colposcopy. All providers were blinded to the results of the previous screening test. The pooled sensitivity of VIA for detecting HSIL was 76.8 percent (95% CI: 74.2–79.4%) and the specificity was 85.5 percent (95% CI: 85.2–85.8%). Across the study centers, the sensitivity ranged from 56.1 to 93.9 percent. The specificity ranged from 74.2 to 93.8 percent. For VILI, the pooled sensitivity for detecting HSIL was 91.7 percent (95% CI: 89.7–93.4%) and the specificity was 85.4 percent (95% CI: 85.1–85.7%). Across the

study centers, the sensitivity for VILI ranged from 76.0 to 97.0 percent. The specificity ranged from 73.0 to 91.3 percent. Overall, VILI appears to be the more sensitive test although the specificities of the two tests are similar.

Sankaranarayanan R, Rajkumar R, Theresa R, et al. **Initial results from a randomized trial of cervical visual screening in South India.** *International Journal of Cancer.* 2004;109:461–467.
Authors conducted a cluster-randomized trial in the Dindigul District of Tamil Nadu, India, to evaluate the efficacy of VIA screening for cervical cancer prevention in an unscreened high-risk population. Villages were randomized into an intervention group that received a single round of VIA screening and a control group. Overall, 30,577 eligible women aged 30 to 59 participated in the intervention arm, and 30,167 eligible women participated in the control arm. In the intervention arm, 2,939 women (9.6%) were screen-positive with VIA and received colposcopy. Of those, 2,777 had biopsy. CIN I was diagnosed in 1,778 women, CIN 2-3 in 222, and cervical cancer (detected by screening) in 69. Between May 2000 and April 2003, 97 women in the intervention arm and 34 women in the control arm were diagnosed with cervical cancer. In the intervention arm, 33 percent of cancers were diagnosed in Stage I compared to in the control arm, where 75 percent of cancers were diagnosed in Stage III (no Stage I cancers were diagnosed in the control group). Authors conclude that VIA-based screening is safe, feasible, and acceptable to women in rural settings. The authors plan to follow the study arms for 10 years, collect incidence data from cancer registries, and compile mortality data from death registries to produce as complete an evaluation as possible of the impact of VIA screening on cervical cancer burden.

Sankaranarayanan, R. et al. **Test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screening in Kerala, India.** *International Journal of Cancer* 106:404–408 (2003).
This article reports the results from a cross sectional study screening 4,444 women in Kerala India with VIA, VILI, and conventional cytology. Colposcopy was conducted on all screened women allowing for the direct calculation of sensitivities, specificities, and predictive values and eliminating the risk of verification bias. Biopsies were performed as indicated on 1,644 women (37%). Screening tests were carried out by three health workers who were qualified trained cytotechnicians, also trained to perform conventional Pap smear and to perform and interpret results of VIA and VILI tests. Findings of CIN 2 or worse, based on colposcopy or biopsy, was defined as "true disease". For VIA the sensitivity and specificity when using a low threshold was 88.6 percent and 78.0% respectively. For high-threshold VIA the sensitivity was 82.6% and specificity was 86.5%. VILI's performance resulted in a sensitivity of 87.2% and a specificity of 84.7%. Finally conventional cytology resulted in a sensitivity of 81.9% and a specificity of 87.8%. The authors conclude that the test characteristics of VIA and VILI in this study signify that both tests are well suited to be used as an alternative to conventional cytology in low-resource settings.

Sankaranarayanan, R., Budukh, A.M., and Rajkumar, R. **Effective screening programmes for cervical cancer in low- and middle-income developing countries.** *Bulletin of the World Health Organization* 79 (10):954–962 (2001).
This article reviews the experiences, challenges, successes, and lessons learned from cervical cancer prevention programs in developing countries. The report draws on data from established screening initiatives in South and Central America (Chile, Colombia, Costa Rica, Cuba, Mexico, Brazil, Peru, and Puerto Rico), sub-Saharan Africa (South Africa, Uganda, Zimbabwe, Burkina Faso, Congo, Ghana, Guinea, Kenya, Mali, Niger, and Nigeria), and South and Southeast Asia (India, Thailand, Singapore, Lao People's Democratic Republic, and China). The authors discuss implications and recommendations for both low-income and middle-income countries. They conclude that, regardless of which screening test will be used, the infrastructure, logistics, finances, and manpower required to establish any organized screening program are too great for many low-income developing countries. VIA, however, could be a viable alternative to detect precancerous lesions in low-income areas where cytology is unavailable. For middle-income developing countries, the authors recommend reorganization of poor-quality cytology programs, with an emphasis on screening high-risk women at least once or twice in their lifetime with a highly sensitive test, and aiming for covering 80 percent of the targeted population.

Sankaranarayanan, R. et al. **Visual inspection with acetic acid in the early detection of cervical cancer and precursors [letter to the editor].** *International Journal of Cancer* 80:161–163 (1999).
This letter to the editor reports on the author's ongoing study comparing the performance of visual inspection with acetic acid (VIA) to cervical cytology in detecting cervical lesions in Kerala, India. Study subjects were 1,351 women age 22 to 70 years (mean age 39). VIA (used by nurses) detected 95.8 percent of dysplasias and cancers; cytology detected 62

percent (VIA detected more mild and moderate dysplasias than cytology). The approximate specificity of VIA was 68 percent and that of cytology was 89.5 percent. The author notes that the effectiveness of VIA in detecting precancerous lesions in this setting, as well as the immediacy of VIA results, make it a potentially attractive case-finding tool in developing-country settings.

Sankaranarayanan, R. et al. **Visual inspection of the uterine cervix after the application of acetic acid in the detection of cervical carcinoma and its precursors.** *American Cancer Society* 83:2150–2156 (1998).
The goal of this study in Kerala, India, was to compare visual inspection of the cervix after the application of acetic acid (VIA) with cytology as methods for detecting cervical cancer and its precursors. Subjects with positive VIA or Pap smear findings as well as subjects with an abnormal-looking cervix (defined by criteria such as bleeding on touch, suspected growth or ulcer, or other cervical abnormality) were invited for diagnostic evaluation by colposcopy and biopsy if appropriate. Of the 3,000 women in the study, 298 (9.9%) were positive on VIA, 307 (10.2%) had atypia or dysplasia on Pap smears, and 182 (6.1%) were positive on both VIA and cytology. An additional 215 women (7.2%) were referred to colposcopy because they were identified as having an abnormal cervix on speculum exam, although they were negative on VIA and Pap. Of the 51 true positive cases, VIA detected 46 (90.1%) and cytology 44 (86.2%). The approximate specificities were 92.2 percent for VIA and 91.3 percent for cytology. The authors conclude that if VIA continues to show satisfactory results, this technique is likely to be useful in developing countries where it is not feasible to introduce cytology screening and in developed countries as an adjunct to improve sensitivity of cervical cytology.

Schneider, D.L. et al. **Cervicography screening for cervical cancer among 8460 women in a high-risk population.** *American Journal of Obstetrics and Gynecology* 180(2, Part 1):290–298 (February 1999).
This study was part of a large, population-based study of the natural history of cervical neoplasia in Guanacaste Province, Costa Rica. It evaluated the effectiveness of cervicography in detecting cervical dysplasia and cancer in 9,062 women age 18 years and older. Two cervigrams were obtained from each woman, in addition to cervical samples for cytological and HPV-DNA testing. The study found that, compared with Pap smears, cervicography was significantly less sensitive, but equally specific. Overall, for detecting high grade SIL or cancer, cervicography had a sensitivity of 49.3 percent and a specificity of 95 percent. In comparison, cytology testing had a sensitivity of 77.2 percent and a specificity of 94 percent. The sensitivity of cervicography was even lower in women over 50 years: 26.9 percent, presumably because of the increased difficulty in viewing the transformation zone in post-menopausal women. While cervicography identified all cancers (many of which were visible on initial physical examination), it detected only 56 of the 117 histologically confirmed cases of high-grade SIL. The authors note that they could increase sensitivity by changing the diagnostic threshold for defining a possible cervigram, but that this would occur at the expense of reduced specificity. In summary, cervicography as used in this study did not appear to be a useful tool for detecting high-grade SIL.

Sellors, J. et al. **Assessment of the cervix after acetic acid wash: Inter-rater agreement using photographs.** *Obstetrics and Gynecology* 99:635–640 (2002).
This study sought to evaluate clinicians' agreement on assessing the cervix after visual inspection with acetic acid (VIA). Three clinicians viewed 144 cervical photographs taken after application of acetic acid and rated them according to VIA categories of negative, positive, or suspicious. Agreement among the pairs of raters was in the moderate to substantial range and was similar to other studies of inter-rater agreement in colposcopy, cervical cytology, and cervical histology.

Spitzer, M. **Cervical screening adjuncts: recent advances.** *American Journal of Obstetrics and Gynecology* 179(2):544–556 (August 1998).
This article reviews six technologies that have been proposed as ways to improve the effectiveness of cervical cancer screening: automated cytologic screening, fluid-based technology (e.g., ThinPrep), HPV testing, cervicography, speculoscopy, and the Polarprobe. The author begins by noting that use of the Pap smear in developed countries has resulted in a major reduction of cervical cancer deaths, and that regular screening of at-risk populations is the best way to reduce cervical cancer incidence. He concludes that use of automated cytologic screening may prove to be an effective approach to primary screening, although wide-scale testing in various settings needs to be implemented. He states that there is insufficient evidence to conclude that fluid-based technologies for producing monolayer slides are superior to standard Pap screening approaches. HPV testing may hold promise for use in multiple test screening protocols, and as a primary screening tool for women older than 35. The author concludes that cervicography and speculoscopy are unlikely

to be useful in large-scale screening efforts. The Polarprobe is an "in development" technology that measures voltage decay and the scattering of light through cervical tissue. It uses a vaginal probe and computer algorithm to process electrical and optical information and determine the likelihood that tissue is abnormal. The author notes that preliminary results with the Polarprobe are promising (see Coppleson, 1994).

Suba, E.J. et al. **De novo establishment and cost-effectiveness of Papanicolaou cytology screening services in the Socialist Republic of Vietnam.** *Cancer* 91(5):928–939 (March 1, 2001).
Using a decision model, this study analyzes the cost-effectiveness of a Pap smear screening program in Vietnam and measures outcomes of life expectance, cervical carcinoma incidence, cost per woman, and cost-effectiveness. The results of the analysis suggest that annual nationwide costs to initiate Pap screening services at five-year intervals will average less that $150,000. Maintenance costs are estimated at $0.092 per woman per year. Cervical cancer incidence and mortality rates could be reduced by 43 percent with five-year screening intervals and 70 percent participation. The author concludes that the data support the cost-effectiveness of establishing widespread Pap smear cervical cancer screening programs, especially since the newer alternative screening techniques are still being tested.

University of Zimbabwe/JHPIEGO Cervical Cancer Project. **Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting.** *Lancet* 353(9156):869–873 (March 13, 1999). Available at: www.thelancet.com if you have a subscription to the *Lancet*. Also available online with commentary (free of charge) through ReproLine at www.reproline.jhu.edu/english/3cc/3lancet/lanceta.htm)
The study involved screening by trained nurse-midwives of almost 11,000 women attending 15 primary care clinics in Zimbabwe and found that, in identifying HGSIL and above, visual inspection with acetic acid (VIA) had a sensitivity of 76.6 percent and a specificity of 64.1 percent. The comparable results for Pap smears were 44.3 percent sensitivity and 90.6 percent specificity. As the accompanying *Lancet* commentary notes, the study provides valuable data on the feasibility and effectiveness of alternative screening approaches in developing-country primary health care settings, and confirmed the relative sensitivity of VIA in comparison to Pap smears in some settings. The commentary also addressed the potential for other new approaches, including HPV screening, and noted the relatively low specificity of VIA in comparison to Pap smears and the potential for overtreatment. The article authors also commented on the ongoing need to carefully assess the implications for programs and patients of a high false positive rate.

Varghese, C. et al. **Cervical cancer control in developing countries: beyond visual inspection.** *Journal of Cytology* 17 (2):97–101 (2000).
This study compared visual inspection (VI) of the uterine cervix with Pap smear results in two populations in South India. VI was found to have low sensitivity and specificity in detecting cervical dysplasia in women attending an out-patient gynecological clinic (28%, and 81%) as well as among a population-based cohort study (64%, and 51%). The authors argue that given the high "false negative" rate for VI, many cases of dysplasia would go undiagnosed. Although VI has been proposed as an appropriate tool in low-resource settings, to do VI properly the facility should have privacy, water, and electricity—all of which may be lacking in many sites. Both diagnostic and treatment services are limited in many sites, and many women fail to comply with referral subsequent to VI. For these reasons, the authors do not support the concept of cervical cancer control through VI in developing countries.

Wesley, R. et al. **Evaluation of visual inspection as a screening test for cervical cancer.** *British Journal of Cancer* 75 (3):436–440 (1997).
The goal of this study was to evaluate the performance of visual inspection by trained paramedical workers in detecting precursor cervical lesions and cancer in resource-poor settings. In the study, 2,843 married women in Kerala, India, were subjected to visual inspection of the cervix and a cytology examination. Of these, 1,279 (45%) and 179 (6.3%) women were found to have a positive visual inspection using the low- and high-threshold criteria. With a low threshold, sensitivity and specificity values for detecting moderate dysplasia and above were 65.8 percent and 55.3 percent respectively; the values for detecting severe dysplasia and above were 71.9 percent and 55.3 percent respectively and 92.3 percent and 55.2 percent respectively for invasive cancer. With a high threshold, the sensitivity values decreased significantly and the specificity increased to about 94 percent. The authors concluded that the use of unaided visual inspection does not appear very promising as a preselection procedure for cytology or as a low technology measure for cervical cancer control and that the procedure is unlikely to be cost-effective.

Winkler, J.L. et al. **Confirmation of cervical neoplasia using a hand-held, lighted magnification device.** *Lancet* 81 (1):35–40 (April 2003).
In low-resource settings where visual inspection with acetic acid (VIA) is being used to test women for cervical lesions, confirmatory methods such as colposcopy are often limited or unavailable. VIA with magnification (VIAM) is being explored as a confirmatory test in some settings. This study assessed the performance of VIAM using the AviScope™ device, a hand-held, monocular scope. A total of 127 women attending 3 colposcopy clinics in Seattle, Washington, had VIAM, colposcopy, and biopsy and endocervical curettage if indicated. All women had been referred for colposcopy because they previously had received a positive Pap smear result. Colposcopically directed biopsy identified 40 women with CIN 2, CIN 3, or carcinoma. The AviScope correctly identified 24 of these 40 women, giving it a sensitivity of 60 percent. Specificity of the AviScope was 69 percent, with it correctly identifying as negative 60 of 87 cases. To date, studies on VIAM have produced conflicting results. The authors of this study caution that although these current results are promising, the actual clinical utility has yet to be determined. The authors suggest, however, that the accuracy of the device could be improved with more extensive provider experience, higher powered magnification, or a different light source.

Zahm, D.M. et al. **Colposcopic appearance of cervical intraepithelial neoplasia is age dependent.** *American Journal of Obstetrics and Gynecology* 179(5):1298–1304 (November 1998).
This study evaluated the effect of a patient's age on results of Pap smears, HPV diagnostics, and colposcopy. The U.S. study evaluated 967 women undergoing routine screening in a gynecologic practice. The key finding of the study was that colposcopic results seemed less reliable in women older than 35 with histologically confirmed cervical intraepithelial neoplasia. Colposcopically "positive" results included acetowhite lesions with a higher degree of opacity, a less regular surface, a longer intercapillary distance, and sharper borders between acetowhite and normal epithelium. Among patients with confirmed intraepithelial neoplasia, 54 percent of women younger than age 35 had colposcopic results consistent with the diagnosis, compared with 32 percent of women age 35 years or older. The authors noted that this result may be linked to the thinner cervical epithelium associated with older age. The study also found higher rates of HPV positivity among women less than 35 years old compared with women 35 years or older.

Top of page

Treatment: evaluation of simple approaches

Alliance for Cervical Cancer Prevention (ACCP). ***Effectiveness, Safety, and Acceptability of Cryotherapy: A Systematic Literature Review.*** Seattle, Washington: PATH (2003). Available at: www.path.org/files/RH_cryo_white_paper.pdf.
This review assesses the available evidence on the effectiveness, safety, and acceptability of cryotherapy for use in treating precancerous cervical lesions. Twelve months after treatment, cryotherapy is approximately 90 percent effective in treating HSIL. Cryotherapy generally produces a lower cure rate for larger lesions and lesions that extend into the cervical canal. Complications associated with cryotherapy are minimal. Data suggest that cryotherapy is safe, with very little risk of major complications such as severe bleeding and pelvic inflammatory disease. The most frequent side effect is a profuse watery vaginal discharge for up to four weeks. Other side effects such as pain and cramping during and after the procedure are generally mild.

Andersen, E.S. and Husth, M. **Cryosurgery for cervical intraepithelial neoplasia: 10-year follow-up.** *Gynecologic Oncology* 45:240–242 (1992).
The goal of this study was to evaluate the long-term results of cryotherapy treatment of CIN. Some 261 patients in Denmark were evaluated over a 5–10 year period following cryotherapy. The authors reported an overall cure rate after 5 years of 83.5 percent. Consistent with findings elsewhere, the cure rates of patients with CIN III were significantly lower than those with CIN I and CIN II. Patients with endocervical involvement had lower cure rate as well. The authors concluded that this long-term study had demonstrated the effectiveness of cryotherapy, but cautioned that it also confirmed the need for other treatment methods for patients with endocervical involvement and for careful follow-up, given the risk of treatment failure.

Bishop, A. et al. **Cervical Dysplasia Treatment: Key Issues for Developing Countries.** *Bulletin of PAHO* 30(4):378–386 (1996).
While in industrialized countries there has been a trend toward more conservative treatment of cervical intraepithelial dysplasia (CIN), a recent survey found this is not true in many less-developed countries. In order to determine the availability of CIN treatment interventions, and to get an overview of current practices, PATH (Program for Appropriate Technology in Health) collected 110 responses from 33 countries. Worldwide, cone biopsy and hysterectomy are used most widely to treat CIN, and are thought by respondents to be most effective for treating severe dysplasia. In many settings, all grades of CIN are treated. Cryotherapy and loop electrosurgical excision procedure (LEEP) are used more often in Asia, the Caribbean, and Latin American than in other areas. These findings suggest that by making low-cost treatment using cryotherapy and LEEP more widely available, more women could be treated and better use made of scarce resources. The results also suggest that current practices involving treatment of all CIN cases should be reevaluated to ensure that the most appropriate and cost-effective treatment protocols are being used.

Bishop, A. et al. ***Cervical Dysplasia Treatment in Developing Countries: A Situation Analysis.*** Seattle: PATH (July 1995).
This extensive review summarizes issues related to cervical dysplasia treatment in developing countries, including appropriate treatment strategies and technologies, a survey of current CIN treatment practices in developing countries, treatment costs analyses, and guidelines for establishing a treatment plan of action.

Burger, R.A. et al. **Single-visit program for cervical cancer prevention in a high-risk population.** *Obstetrics and Gynecology* 86(4, Part 1):491–498 (October 1995).
The three goals of this study were to screen and treat—in a single visit—women at increased risk for cervical cancer, to determine the feasibility of this single-visit approach, and to evaluate its acceptability to study participants. Some 126 women in southern California, USA, were recruited for the study through Spanish-language media; all had at least one risk factor for cervical cancer and most reported some barrier, usually cost, to obtaining health care. The single-visit program included a Pap smear; immediate cytologic evaluation; and, for those with cytology results consistent with low- or high-grade SIL, a loop electrosurgical excision or biopsy. Patients who underwent excision or biopsy were asked to return in two weeks for evaluation. The study found the See and Treat approach to be feasible and well accepted. Overtreatment (i.e., no histologic abnormality identified in the excised specimen) occurred in an estimated 5 percent of patients, a figure the authors deemed acceptable given the trade-off of convenient, effective, inexpensive care that does not rely on follow-up visits.

Flannelly, G. et al. **A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia.** *British Journal of Obstetrics and Gynecology* 104(6):718–722 (June 1997).
The goals of this study were to examine the long term efficacy of large loop excision of the transformation zone (LLETZ) in the treatment of CIN and to evaluate the relative diagnostic merits of colposcopy and cytology in the follow up of these women. The study examined cytology, colposcopy, and histology records of the first 1,000 women treated with LLETZ in the Colposcopy Clinic, Aberdeen Royal Infirmary, Scotland, from 1989 to 1991. A total of 2,812 woman years of follow-up were obtained. The recurrent rate of CIN was 27/1,000 woman years and the cumulative recurrent rate at four years was 10.1 per 100 women. Of the women with abnormal colposcopy and proven CIN, 47 percent had a concurrent smear that did not show dyskaryosis. The authors concluded that LLETZ is effective in treatment for CIN, and colposcopy was useful in the follow-up of these woman and expedited the treatment of persistent disease. They recommend that any follow-up protocol should include a colposcopic assessment and cytological follow up for at least four years following treatment.

Hulman, G. et al. **Frequency of cervical intraepithelial neoplasia following large loop excision of the transformation zone.** *Journal of Clinical Pathology* 51:375–377 (1998).
This retrospective study of 669 women in the United Kingdom assessed the risk of persistent/recurrent CIN following treatment by large loop excision of the transformation zone (LLETZ). With LLETZ biopsies, physicians must preserve as much healthy tissue as possible while ensuring that the CIN has been completely removed. Since doctors may be unable to determine the full extent of CIN presence in the endocervical canal, LLETZ biopsies may be incomplete or equivocal.

This study found that the persistence/recurrence of CIN was significantly lower in cases where complete excision had occurred. The study also found that persistence/recurrence increased by grade of CIN (for example, from 6.7 percent of patients with CIN1 to 21.7 percent of patients with CIN3). The authors conclude that physicians should carefully follow up on patients with either high-grade CIN or incomplete or equivocal excision.

Keijser, K. et al. **Diathermy loop excision in the management of cervical intraepithelial neoplasia: diagnosis and treatment in one procedure.** *American Journal of Obstetrics and Gynecology* 166(4):1281–1287 (April 1992).
This Dutch study found diathermy loop excision (another term for LEEP) to be an effective, efficient, and inexpensive technique for diagnosis and treatment of CIN. In the study, 424 women found to have slight to severe dysplasia (CIN grades 1–3) were treated with a stainless steel, rectangular loop used to excise lesions from the cervix and endocervical canal. Over a three- to eight-year follow-up period (median 4.8 years), the study found an overall cure rate of over 92 percent — 81 percent after one treatment, the remaining 11 percent after two or three treatments. The authors characterized these results as in the same range with cryocoagulation and laser techniques, but noted that diathermy loop excision is an outpatient method, requiring no general anesthesia and far less training and expensive equipment. They also found diathermy loop excision to be effective for treatment of lesions in the endocervical canal and calculated the method's diagnostic accuracy rate at 99 percent, with no evidence of an effect on fertility or pregnancy outcome.

Kleinberg, M.J. et al. **A cost-effectiveness analysis of management strategies for cervical intraepithelial neoplasia grades 2 and 3.** *American Journal of Obstetrics and Gynecology* 188:1186–1188 (2003).
This article reports the results of an analysis of the cost-effectiveness of various management strategies for CIN 2 and 3, including observation, cryotherapy, loop electrosurgical excision procedure (LEEP), carbon dioxide laser ablation, cold-knife conization, and total vaginal hysterectomy. The analysis was conducted using a decision model for a hypothetical cohort of 100,000 women with CIN 2 or CIN 3. Costs were based on US dollars in 2001. Outcome probabilities used in the model were based on available published literature. Three strategies proved cost-effective for managing CIN 2 and CIN 3: cryotherapy, LEEP, or total vaginal hysterectomy. Of the three, cryotherapy was the least expensive while still offering an effective treatment. Cryotherapy had a total cost for CIN 2 of US$41 million with a cure rate of 94.9% (1,454 cancers prevented) compared to LEEP's total cost of $75 million and cure rate of 95.9% (1473 cancers prevented). For CIN 3 cryotherapy's total cost was $46 million, with a cure rate of 91.3 % compared to LEEP's cost of $91 million and cure rate of 93.9%. The authors suggest that cryotherapy's cost and effectiveness make it an appropriate treatment choice in less-developed settings.

Megevand, E. et al. **Can cervical cancer be prevented by a see, screen, and treat program? A pilot study.** *American Journal of Obstetrics and Gynecology* 174(3):923–928 (March 1996).
The goal of this prospective study was to determine the feasibility of providing cervical cancer diagnosis and treatment on site through a mobile clinic at the time of screening or with minimal delay. A total of 5,054 women attended a mobile clinic in Cape Town, South Africa, where they received a free Pap smear and information about cervical cancer and its prevention. In phase 1 of the study, women diagnosed with high-grade squamous intraepithelial lesion were referred to a nearby clinic for colposcopy and treatment. In phase 2, colposcopy and treatment were given on site. Thirty-four percent of 86 women with high-grade lesions in phase 1 attended the colposcopy clinic and received proper treatment (default rate 66%). In contrast, 97 percent of 33 women with high-grade lesions in phase 2 attended the clinic and received proper treatment (default rate 3%). The authors emphasized that education is an essential component in any successful screening program. They concluded that most women will undergo colposcopy and treatment when screening results are obtained quickly and when a colposcopy facility is located at the screening site.

Mitchell, M.F. et al. **A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix.** *Obstetrics & Gynecology* 92(5):737–744 (1998).
The goal of this randomized clinical trial was to compare the complications and cure rates of three methods of treating squamous intraepithelial lesions (SIL) of the cervix. The analysis compared data from 390 women randomly assigned to treatment with cryotherapy, laser vaporization, or loop electrosurgical excision after grouping by SIL grade, endocervical gland involvement, and lesion size. Patients were followed for a period of 6–37 months with a mean of 16 months. The authors found no statistically significant differences in the complication rates, the persistence of disease within six

months of treatment, or the recurrence of disease at least six months after treatment among the three groups. They did find that the risk of persistent disease was eighteen times higher (risk ratio [RR], 18.9; 95 percent confidence interval [CI], 3.2, 110.6) among women with lesions more than two-thirds the size of the surface area of the cervix. They also found that recurrent disease was higher among women who were 30 years and older (RR, 2.1; 95% CI = 1.2, 4.3), women positive for HPV types 16 or 18 (RR, 2.1; 95% CI = 1.1,4.0), and women with a prior history of treatment for CIN (RR, 2.1; 95% CI = 1.1, 3.9). The authors concluded that these three treatment methods had comparable rates of success and complications for the period of follow-up in this study.

Olatunbosun, O.A. et al. **Outcome of cryosurgery for cervical intraepithelial neoplasia in a developing country.** *International Journal of Gynecology and Obstetrics* 38:305–310 (1992).
In this Nigerian study, 73 women diagnosed with CIN were treated by cryosurgery. After a five-year follow-up period, the cure rate was 90 percent, excluding 22 women lost to follow-up. The authors characterized these results as comparable with those reported for other destructive methods and commended cryosurgery as a simple, low-cost, outpatient treatment approach, without serious side-effects or effects on pregnancy outcome. They emphasized, however, the importance of proper pretreatment evaluation and the need for long-term follow-up of patients. They also recommended against the use of cryosurgery for CIN with glandular involvement, given its limited depth of destruction.

Paraskevaidis, E. et al. **Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins.** *Obstetrics and Gynecology* 95(6):828–831 (June 2000).
The goals of this case-control study in Greece were to determine the risk of cervical intraepithelial neoplasia (CIN) recurrence in women treated with large loop excision, and to determine risk factors that could lead to better follow-up care. Women treated with loop excision for CIN with clear margins who had adequate follow-up and in whom no subsequent lesions were found (controls) were compared with women who presented with subsequent CIN (cases). Of the 635 women studied, 31 (4.9%) were diagnosed with subsequent lesions. Women over age 40 were found to be at increased risk for recurrence of CIN. The study also found that women with satellite lesions detected before initial treatment and those with glandular involvement were significantly more likely to have a recurrence. The study concluded that large loop excision treatment for women with clear margins and no risk factors is very effective. Follow-up for these women could be less intensive and they could return to normal screening after 12 months. Women who have clear margins but also have any of the identified risk factors should continue with current follow-up protocols.

von Gruenigen, V. et al. **Bacteriology and Treatment of Malodorous Lower Reproductive Tract in Gynecologic Cancer Patients.** *Obstetrics and Gynecology* 96(1):23–27 (July 2000).
This prospective case-cohort study evaluated the bacteriology of lower reproductive tract cancers, and the impact of treatment on the quality of life of patients. Gram stain, saline preparations, tumor pH, and anaerobic and aerobic tumor cultures were taken from thirteen patients with malodorous gynecologic cancers, and thirteen with nonmalodorous cancers at the University of Texas Southwestern Medical Center at Dallas. The majority of these (21) had cervical cancer. Most patients with odor had bacterial vaginosis (8 of 13, or 62%). All patients with malodorus tumors were treated with topical metranidazole for seven days. Of the eight patients diagnosed with bacterial vaginosis prior to treatment, none had bacterial vaginosis after treatment, and seven of the thirteen reported no odor after treatment. This small, non-controlled study indicates that patients with malodorous pelvic tumors might benefit from treatment with the topical antibiotic metranidazole.

Top of page

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links

- Presentations
- Spanish Edition

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Annotated Bibliography

This is **page 3** of the Cervical Cancer Prevention Annotated Bibliography. This page contains:

To access more bibliographic entries, visit page 1 or page 2, or return to the complete list of topics covered in the Cervical Cancer Annotated Bibliography. Be sure to use the Glossary if you are unfamiliar with any of the terms on this page.

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Cervical cancer and HIV

Abercrombie, P.D. and Korn, A.P. **Lower genital tract neoplasia in women with HIV infection.** *Oncology* 12 (12):1735–1739 (December 1998).
This article reviews the current body of knowledge about lower genital tract neoplasia in HIV-infected women. Issues discussed in the article include human papillomavirus (HPV) infection in HIV-infected women, lower genital tract neoplasia, and cancer. The authors recognize that knowledge about the pathophysiology and clinical management of lower genital tract neoplasia in HIV-infected women is incomplete, and that more research in this area is needed. Regular performance of cervical Pap smears can be of critical importance. Careful examination of the entire lower genital tract of HIV-infected women is crucial, because of the multifocal nature of HPV-related neoplasms. The authors recommended that women who have high-grade intraepithelial neoplasia or cervical cancer be offered testing for HIV infection.

Chirenje, Z.M. et al. **Association of cervical SIL and HIV-1 infection among Zimbabwean women in an HIV/STI prevention study.** *International Journal of STD & AIDS* 13:765–768 (2002).
This article presents results from a cross-sectional study of the association of cervical squamous intraepithelial lesions (SIL) and HIV-1 infection in Zimbabwe. Among the 554 women in the study, the prevalence of HIV-1 was 36.8 percent. Compared to HIV-negative women, HIV-infected women had twice the risk of having abnormal cervical cells (relative risk 2.47, odds ratio 10.14, $P < 0.001$), The prevalence of both low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions was associated with HIV infection; this association was statistically significant. These results agree with other studies showing that HPV infection and the presence of cervical lesions are associated with HIV infection. The authors suggest that, in resource-poor settings, careful decisions about resource allocation must be made because of the many competing health needs of HIV-positive women. In Zimbabwe, although HIV-infected women have higher rates of HSIL, the Zimbabwe National Cancer Registry has not recorded an increase in invasive cervical cancer cases. Due to scarcity of resources and anti-retroviral drugs, the authors hypothesize that many HIV-infected women may be dying of other opportunistic infections prior to presenting with invasive cervical cancer.

French, A.L., Kirstein, L.M., Massad, L.S., et al. **Association of vitamin A deficiency with cervical squamous intraepithelial lesions in human immunodeficiency virus-infected women.** *Journal of Infectious Diseases* 182:1084–1089 (October 2000).
This study examined the association between vitamin A deficiency and the development of cervical squamous intraepithelial lesions (SILs) in 1,314 HIV-infected women. Retinol (vitamin A) concentrations were measured at a baseline visit and compared to cervical samples (Pap smears and cervicovaginal lavage fluid). At baseline 204 women had retinol levels that met the definition of vitamin A deficiency (<1.05umol/L). Pap smear results showed 216 women with SILs. Multivariate statistical analyses suggest low retinol concentrations were independently associated with SILs (OR 1.63; $P = .04$). The analysis was repeated in a subset of women who had tested positive for HPV DNA. Mulitvariate analysis again showed an association between retinol deficiency and cervical SILs (OR 1.75; $P = .02$). These findings, which contradict several earlier studies, suggest that vitamin A deficiency in HIV-infected women may play a role in the development of cervical SILs and suggest that further study of this association is necessary.

Fruchter, R.G. et al. **Is HIV infection a risk factor for advanced cervical cancer?** *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 18(3):241–245 (July 1, 1998).
The goal of this study was to compare HIV-infected and HIV-negative women with invasive cervical cancer with respect to predictors of advanced disease. The study compared 28 HIV-infected and 132 HIV-negative cervical cancer patients with regard to stage of disease, demographic and behavioral variables, and risk factors for advanced disease. Results from a retrospective analysis of the data showed that HIV-infected women had a fivefold greater rate of cervical intraepithelial neoplasia or unevaluated abnormal smears than the HIV-negative women. A univariate analysis indicated that HIV infection was associated with a threefold increase in advanced-stage cervical cancer. However, a multiple logistic regression analysis showed that the major predictors of advanced cervical cancer in HIV-infected and HIV-negative women were similar and that only lack of cytologic screening and prolonged duration of symptoms were significant predictors of advanced disease. The authors stated that it is likely that a large proportion of HIV-infected women with cervical cancer acquire HIV infection after the initiation of the neoplastic process rather than as a result of immunodeficiency, demonstrating an association of the common behavioral risk factors of the two diseases rather than a causal effect of HIV immunodeficiency.

Gichangi, P.B. et al. **Impact of HIV infection on invasive cervical cancer in Kenyan women.** *AIDS* 17:1963–1968 (2003).
Data on the interaction between HIV and invasive cervical cancer (ICC) are scarce. In this case-control study, authors examine this association in a population of Kenyan women where the prevalence of both HIV and ICC are substantial. The Cases were recruited from women with cervical cancer at the radiotherapy unit in Kenyatta National Hospital. Controls were women with uterine fibroids diagnosed by ultrasound. After controlling for confounding factors of educational level, number of partners, and previous history of an STD, women with invasive cervical cancer who also were HIV-positive were on average 10 years younger than HIV-negative women with invasive cervical cancer. In fact, ICC patients less than 35 years of age were 2.6 times more likely to be HIV-positive than patients with uterine fibroids of the same age. HIV-positive ICC patients also had greater risk of having poorly differentiated tumors as compared to HIV-negative ICC patients (77% vs. 53%; OR, 3.1; P=0.038), which is indicative of a poor prognosis.

La Ruche, G. et al. **Squamous intraepithelial lesions of the cervix, invasive cervical carcinoma, and immunosuppression induced by human immunodeficiency virus in Africa.** *Cancer* 82(12):2401–2408 (June 15, 1998).
Squamous intraepithelial lesions (SILs) are associated with human immunodeficiency virus (HIV), but the factors associated with SILs and cervical cancer, and their prevalence must be considered in context. This study screened 2,198 women from three outpatient gynecological clinics in Abidjan, Côte d'Ivoire, for cervical disease and HIV infection. The prevalence of HIV infection was 21.7 percent, and 11.7 percent had dysplasia or neoplasia (7.6 percent low grade SILs, 3.3 percent high grade SILs, and .8 percent invasive cervical cancer). Multivariate analysis found that the factors associated with low grade SILs were: HIV-1 seropositivity, age less than 24 years, parity greater than one, consultation for genital infection, and no use of oral contraceptives in the past. For high-grade SILs, the factors were HIV-1 seropositivity, chewing tobacco use, low educational level, and parity greater than one. Cervical cancer was associated with age over 33 years, parity greater than three, and illiteracy. Cancer was associated with HIV-2 infection, but not HIV-1 infection. The factors associated with precancerous and cancerous lesions are different. HIV-positive women should receive screening for cervical cancer, and women with cervical cancer should be offered HIV testing. However, cervical cancer screening should not depend on HIV screening because the requirements of the two programs differ. Cervical cancer screening could be directed toward women with low educational levels or multiparity or both, as indicated by the risk factors identified in this study.

La Ruche, G. et al. **Human papillomavirus and human immunodeficiency virus infections: relation with cervical dysplasia-neoplasia in African women.** *International Journal of Cancer* 76:480–486 (1998).
The goal of this study was to assess the factors associated with squamous intraepithelial lesions (SILs) and invasive cervical cancer, with special attention to human immunodeficiency virus (HIV) and human papillomavirus (HPV). Women were recruited from three outpatient gynecology clinics of Abidjan, Cote d'Ivoire, and screened for cervical abnormalities. The women were placed into three case-control groups: 151 women with low-grade SILs and 151 controls, 60 women with high-grade SILs and 240 controls, and 13 women with invasive cancer and 65 controls. Results from multivariate analyses showed that factors associated with low-grade SILs were HPV positivity, HIV-1 seropositivity, and parity greater than 3. Factors associated with high-grade SILs were HPV positivity, chewing tobacco, HIV-1 seropositivity, and illiteracy. The only factor associated with invasive cancer was HPV positivity. The results show that, in HIV-infected women, SILs occurred at an early stage of HIV disease. Women infected with both HIV and HPV were at a much higher risk of SILs than women infected with either of the two viruses separately. Based on the study findings, the authors suggest that cervical screening could be directed preferentially to women with low educational levels or women of high parity.

Leroy, V. et al. **Cervical dysplasia and HIV type 1 infection in African pregnant women: a cross sectional study, Kigali, Rwanda.** *Sexually Transmitted Infections* 75:103–106 (1999).
The goal of this study was to determine the prevalence of cervical squamous intraepithelial lesions (SILs) and their association with HIV-1 infection and immunodeficiency among pregnant women in Kigali, Rwanda. A total of 103 HIV-positive and 107 HIV-negative women participated in the study. The participants were recruited at the maternity ward of the Centre Hospitalier de Kigali. At inclusion, the women were screened for sexually transmitted infections (STIs) including syphilis, gonorrhea, chlamydia, and trichomoniasis. CD4 cell counts were measured and Pap smears were performed. The study results showed that the prevalence of SILs was significantly higher in HIV-infected women than in HIV-negative women: 24.3 percent versus 6.5 percent, respectively. Furthermore, SIL-positive women tended to have more STIs than SIL-negative women (37.5% and 24.7%, respectively), but this did not reach a statistical difference. The authors conclude that the prevalence of SILs was high in this population of pregnant women with high STI/HIV prevalence. They note that this cross-sectional study cannot establish a causal relation between HIV infection and SILs. Other factors such as age, age at first intercourse, parity, STIs, and number of sexual partners may be confounding factors in the analysis of this association.

Luque, A.E. et al. **Association of human papillomavirus infection and disease with magnitude of human immunodeficiency virus type 1 (HIV-1) RNA plasma level among women with HIV-1 infection.** *Journal of Infectious Diseases* 179:405–409 (June 1999).
The goal of this cross-sectional study was to evaluate the relationship between plasma HIV-1 RNA levels and coincident

cervical infection and disease caused by human papillomaviruses (HPVs). A total of 93 women recruited from the University of Rochester's Strong Memorial Hospital enrolled in the study. The women underwent a standardized history and physical examination that included a gynecologic history and pelvic examination. The study results showed that HIV-1 RNA plasma levels of greater than 10,000 copies/mL were highly associated with high-risk HPV DNA in cervical specimens. In addition, similar HIV-1 RNA plasma levels were associated with abnormal Pap smears. Eighty-one percent of women with high-risk HPV cervical infection had abnormal Pap smears. Among the women with detectable HPV DNA, the most frequent abnormality reported in Pap smears was low-grade SIL on specimens from 54 percent of patients with high-risk HPV DNA. The authors conclude that measurements of HIV-1 RNA plasma levels may help to identify a subgroup of HIV-infected women at increased risk for cervical HPV infection and disease and that women with moderate to high levels of plasma HIV-1 RNA may profit from aggressive gynecologic monitoring.

Palefsky, J.M. et al. **Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women.** *Journal of the National Cancer Institute* 91(3):226–236 (February 3, 1999).
The goal of this study was to determine the prevalence of and risk factors for cervicovaginal HPV infection in HIV-positive women. A total of 1,778 HIV-positive and 500 HIV-negative women were recruited from a pool of women enrolled in the Women's Interagency HIV Study. The study results confirmed earlier observations that HPV infection is significantly more common among HIV-positive women than in high-risk HIV-negative women. Compared with HIV-negative women, HIV-positive women with CD4 cell count of less than 200/mm^3 were at the highest risk of HPV infection, regardless of HIV RNA load, followed by women with a CD4 cell count greater than 200/mm^3 and an HIV RNA load greater than 20,000 copies/mL, and women with CD4 count greater than 200/mm^3 and an HIV RNA load less than 20,000 copies/mL. Other risk factors among HIV-positive women included racial/ethnic background (African American versus Caucasian, OR = 1.64), current smoking (yes versus no, OR = 1.55), and younger age (age <30 years versus ≥40 years, OR = 1.75). The study results suggest that detection of HPV in HIV-positive women more likely reflects either reactivation or persistence of pre-existing HPV types rather than recent HPV acquisition.

Tate, D. and Anderson, R. **Recurrence of cervical dysplasia among women who are infected with the human immunodeficiency virus: a case-control analysis.** *American Journal of Obstetrics and Gynecology.*186(5, Part 1):880–882 (2002).
This case-control study compared cervical dysplasia treatment outcomes for 43 HIV-positive women and 103 HIV-negative women. The women received cryotherpy, laser ablation, LEEP, conization, or hysterectomy as treatment for CIN. For all treatment modalities, women who were HIV-positive had higher recurrence rates than HIV-negative women (73% versus 27%; *P* = .019). Overall, for all treatment modalities, patients with CD4 cell counts <200 had higher recurrence rates than women with higher CD4 counts.

Wright, T.C. et al. **Human immunodeficiency virus 1 expression in the female genital tract in association with cervical inflammation and ulceration.** *American Journal of Obstetrics and Gynecology* 184(3):279–285 (February 2001).
This study quantified the change in HIV-1 RNA shedding in women who had been treated for cervical squamous intraepithelial lesions. HIV-1 RNA levels in the cervicovaginal secretions were measured before and after treatment in 14 HIV-positive women with cervical lesions. At two to four weeks post-treatment, when the cervix visually was still inflamed and ulcerated, cervicovaginal HIV-1 shedding had increased as much as 10,000 fold (from 1.0 to 4.4 log 10; mean log 10 increase was 2.3). Between 8 and 14 weeks after treatment, when the cervix had healed, HIV-1 RNA levels had returned to pre-treatment levels. Additional tests were performed to rule out contamination of the cervicovaginal secretions by HIV virus in the found in the blood and it was concluded that blood was an unlikely explanation for the significant increase of HIV-1 RNA found in the genital secretions. The authors recommend that HIV positive women undergoing treatment for cervical lesions should be counseled to abstain from sexual intercourse for at least four weeks following the treatment to avoid transmitting HIV to their partners.

Top of page

Cost-effectiveness and cost implications

Brown, A.D., Raab, S.S., Suba, E.J., et al. **Cost-effectiveness studies on cervical cancer.** *Acta Cytologica* 45:509–514 (2001).
This article reviews recommendations generated at the International Consensus Conference on the Fight Against Cervical Cancer. These recommendations include: (1) Cost-effectiveness analyses should, whenever possible, use a reference case to report baseline results. (2) Cost-effectiveness analyses should use a single standard of evidence when evaluating interventions. (3) Further research is necessary to provide information on questions including quality of life after receiving a false positive result and the costs of various aspects of screening and treatment strategies. (4) Further research on cost-effectiveness is necessary in developing countries. (5) Detailed methodology, including assumptions used in the cost-effectiveness model, should be made available in an accessible place such as the Internet. (6) Comparisons of available models should be made. (7) Conflicts of interest of researchers should be disclosed, with subsequent opportunity for publication.

Goldie, S.J., Kuhn, L., Denny, L., et al. **Policy analysis of cervical cancer screening in low-resource settings: clinical benefits and cost-effectiveness.** *JAMA* 285(24):3107–3115 (June 27, 2001).
This study utilizes a mathematical model to compare the clinical benefits and cost-effectiveness of various screening and treatment strategies for cervical cancer prevention, including HPV DNA testing, direct visual inspection (DVI)—also commonly referred to as visual inspection with acetic acid (VIA)—and cytology. Data inputs include data from an existing South African study being implemented by EngenderHealth, Columbia University, and the University of Cape Town; existing schedules and surveys of fees; and other literature. Policy analysis using this model suggests that, using a hypothetical population of previously unscreened South African women, a single lifetime screening followed with immediate treatment at age 35 offered the best balance of costs and benefits. As compared to no screening, DVI followed with immediate treatment with cryotherapy can decrease subsequent cervical cancer incidence by 26 percent and was cost saving. The most effective strategy, HPV testing followed by a second visit for treatment, reduced cervical cancer incidence by 27 percent and cost $39/YLS (years of life saved). One-visit strategies, however, as compared to two-visit or three-visit strategies, reduced costs and loss to follow up. Authors note that cost-effectiveness analyses are but one important input into a policy decision, and cultural norms, health infrastructure, costs for equipment, supplies, and training may all be country- or region-specific and will need to be considered as well. This policy analysis, however, has important implications for decisions around cervical cancer screening in developing countries, offering countries with limited resources evidence of cost-effective screening and treatment strategies.

Top of page

Client perceptions

Adanu, R.M.K. **Cervical cancer knowledge and screening in Accra, Ghana [letter to the editor].** *Journal of Women's Health & Gender-Based Medicine* 11(6):487–488 (2002).
In this letter, the author discusses the results from a questionnaire on cervical cancer knowledge and screening practices that was completed by 175 well-educated women in Accra, Ghana. Women participants were categorized as medical students, non-medical undergraduate students, nurses, and senior university workers. Among these 175 women, 93 percent said they had heard of cervical cancer, although only 37 percent had adequate knowledge of the disease. Only 39 percent of women had adequate knowledge of Pap smears and, of those, only 8.5 percent had ever had a Pap smear. Medical students and nurses had the most knowledge of cervical cancer and Pap smears, while actual Pap smear use was highest among university staff. The author discusses how the level of knowledge is not necessarily translated into use. The author highlights the need for an organized cervical cancer screening program that would includes better public education of nonmedical personnel and increased initiative from medical doctors to perform routine Pap smears.

Ajayi, I.O. and Adewolfe, I.F. **Knowledge and attitude of general outpatient attendants in Nigeria to cervical cancer.** *Central African Journal of Medicine* 44(2):41–43 (1998).
This cross-sectional study of women between the ages of 20 and 65 investigated Nigerian women's knowledge about

cervical cancer, their source of information, and their general attitude about cancer. A total of 254 women were randomly selected from patients and accompanying persons attending a general outpatient clinic at a tertiary hospital in Ibaadan, Nigeria, to complete a structured questionnaire. The authors found that 90 percent of these women had heard of cancer (most commonly breast cancer [64.5 percent]). Only 15 percent had heard of cancer of the cervix. Media and peers were the major sources of information on cancer. Over half of the respondents had no knowledge of the description of cervical cancer, clinical presentation, or causes. The authors conclude that knowledge of cervical cancer is poor and that there is a need to educate women about cervical cancer and its early warning signs in Nigeria.

Dzuba, I.G. et al. **The acceptability of self-collected samples for HPV testing vs. the Pap test as alternatives in cervical cancer screening.** *Journal of Women's Health & Gender-based Medicine* 11(3):265–275 (2002).
This study evaluated the acceptability of self-collected samples for HPV testing as compared to the Pap test among 1,069 women in Mexico. Women were asked questions about their experiences with both methods of screening and ranked each test on discomfort, pain, embarrassment, privacy, perception of treatment during the Pap test, and clarity of the instructions for the self-collection for HPV. Results showed that overall the women rated the self-collection method as more acceptable to the Pap smear. When women reported a preference for a test, they more often chose the self-sampling method. The reasons for preferring the self-sampling method included less discomfort and less embarrassment. Women indicated no difference in the level of pain or level of privacy experienced during the two tests. Authors suggest that offering self-collection could increase participation in cervical cancer screening among women who are uncomfortable with Pap tests.

Fylan, F. **Screening for cervical cancer: a review of women's attitudes. Knowledge, and behaviour.** *British Journal of General Practice* 48:1509–1514 (August 1998).
The article reviews the psychological consequences of receiving an abnormal cervical smear result and undergoing secondary screening and treatment, and examines reasons for women's nonparticipation in screening programs. Reasons for nonparticipation include administrative failures, unavailability of female screeners, inconvenient clinic times, lack of awareness of the test's indications and benefits, considering oneself not to be at risk of cervical cancer, and fear of embarrassment, pain, or the detection of cancer. Receiving an abnormal result and referral for colposcopy causes high levels of distress owing to limited understanding of the meaning of the smear test; many women believe the test aims to detect existing cervical cancer. The article discusses ways in which health professionals can increase their patients' participation in screening programs and minimize the distress experienced by women who require secondary screening and treatment.

Holroyd E, Twinn S, Adab P. **Socio-cultural influences on Chinese women's attendance for cervical screening.** *Journal of Advanced Nursing.* 2004;46(1):42–52.
Authors investigated the sociocultural influences on women's attendance for cervical cancer screening in Hong Kong. Data were gathered from 10 focus groups with 54 previously screened and unscreened women and from interviews with 28 Hong Kong doctors. The focus groups revealed several themes. For women who had sought screening, the decision was more often prompted by marriage or childbirth rather than self-initiated for health protection. Having a friend or relative with cancer also influenced women's decisions to seek screening. The focus groups identified a preference for female providers among both screened and unscreened women. Perceived risk factors for cervical cancer identified by the women included promiscuity, marriage, youth and old age, poor personal hygiene of husbands and selves, and the use of tampons. Unscreened women in particular tended to associate seeking health services with illness, not prevention. Barriers to attending screening included time away from work and family, costs, embarrassment, and perceptions of pain. Data from the interviews with doctors showed doctors perceived low educational status, poverty, and lack of knowledge of cervical cancer as barriers to women attending screening. They also described fatalism, modesty, and low perceived susceptibility as factors affecting women's intentions to seek screening. Finally, several doctors suggested that long waits for services at the clinic posed barriers for women who do not have the time to come for several visits. Authors conclude that there is a need for ensuring all cervical cancer screening programs are conducted in culturally sensitive ways. They recommend education for providers so that they can address the social and cultural factors in the community that act as barriers and can better promote seeking preventive health care and cervical cancer screening services.

Idestrom, M. et al. **Women's experience of coping with a positive Pap smear: a register-based study of women with**

two consecutive Pap smears reported as CIN 1. *Acta Obstetrica et Gynecologica Scandinavica* 82(8):756–761 (August 2003).
This study examines how receiving positive Pap smear results affects women's daily lives and decisions to return for follow-up and treatment. Questionnaires were mailed to 324 Swedish women who five years prior had received two consecutive positive Pap smears showing CIN 1 and should have returned for investigative follow-up. Of these women, 242 (74%) returned the questionnaire. The mean age of women completing the questionnaire was 45 years (range 24–81 years). Two hundred and thirty-three women (96%) returned for follow-up, and for 178 of these women follow-up included a biopsy. The majority of women reported a good or positive experience with the follow-up exams, with older women more frequently reporting a positive experience than younger women. Overall, however, 142 women (59%) reported worry and anxiety over receiving positive Pap smear results and over the significance of the positive result. Twenty women (8%) reported a continued negative effect on their sexuality and their sexual relationships. Most women reported receiving information about Pap smears and dysplasia from their doctor or midwife. Less frequently reported sources of information included media, the health care system (written information), school education, and friends and family. The authors conclude that better sources of information are needed because many women were not receiving the message that mild dysplasia was not a diagnosis of cancer, causing undue worry and stress in their lives when they received a positive Pap smear result.

Jameson, A. et al. **Barriers to Pacific women's use of cervical screening services.** *Australian and New Zealand Journal of Public Health* 23(1):89–92 (1999).
This study explored perceived barriers to cervical screening information services from the perspective of Pacific Island women living in New Zealand. Face-to-face, in-depth interviews based on a snowballing technique were used to assess attitudes among 20 Pacific women. Women identified numerous barriers, including a perception that Pacific women were being defined as socially problematic, a belief in the sacred nature of human sexuality, anxiety about a lack of confidentiality within community groups, and the perceived relationship between cervical smears and sexual activity. Study participants also voiced a strong preference for formal and interpersonal rather than informal sources of information. Formal sources included doctors, nurses, clinics, hospitals, and women's health centers. Talking with female rather than male professionals was strongly preferred. Women also agreed that the preferable role of a Pacific Island health professional would be in disseminating information, rather than taking Pap smears. They recommended that multi-racial images of women be used in advertising, illustrating that Pap smears are necessary for all women.

Lauver, D. et al. **Women's uncertainties, coping, and moods regarding abnormal Papanicolaou results.** *Journal of Women's Health & Gender-based Medicine* 8(8):1103–1112 (1999).
The goal of this study was to understand the process of coping with the news of abnormal cervical cancer screening results. The specific aims were to (1) compare women's uncertainty about the implications of abnormal Pap tests and their psychological distress over time, and (2) describe relationships among uncertainty, perceived coping ability, coping strategies that were used and helpful, and psychological distress. Women were recruited from January 1995 to March 1996 from multiple health clinics. Seventy-five women agreed to participate and completed the initial telephone interview after hearing the news of their abnormal Pap tests. Forty women completed follow-up questionnaires before their colposcopy, and 35 of these women also completed questionnaires after their colposcopy follow-up. The study results showed that women's uncertainty about abnormal Pap test results decreased over time. Negative mood scores, reflecting psychological distress, did not change over time. Uncertainty about Pap tests, ambiguity about cancer, and perceived inability to deal with Pap test results were positively related. The coping strategy of catharsis (that is, expression of emotions) was associated with greater psychological distress (high negative mood scores) after learning of the news, but acceptance was associated with less psychological distress. The authors conclude that clinical interventions can address uncertainty and promote coping strategies such as relaxation, acceptance, and diversion to reduce psychological distress among women with abnormal cervical smear results.

Lazcano-Ponce, E.C. et al. **The positive experience of screening quality among users of a cervical cancer detection center.** *Archives of Medical Research* 33:186–192 (2002).
This study used a population-based survey in the State of Morales, Mexico, to examine the factors associated with higher levels of use of the Pap test. Interviews were conducted with 3,197 randomly selected households, among which 2,094 women had previously had a Pap test and were included in the study. Factors associated with greater use of Pap smear screening services included a previous positive experience with the services, a higher level of education for the head of

household, the use of two or more family planning methods, and the understanding of why the screening was necessary. Women who reported that the privacy during the Pap smear screening was acceptable and women who reported that the information given for follow-up care had been good were more likely to have had two or more Pap tests. Authors conclude that in areas of Mexico where cervical cancer screening is ineffective, programs should focus on improving quality of care as a key component of increasing utilization of screening services.

Lazcano-Ponce, E.C. et al. **Barriers to early detection of cervical-uterine cancer in Mexico.** *Journal of Women's Health* 8(3):399–408 (1999).
This qualitative study of barriers to early detection of cervical cancer included four focus groups—two in the urban setting of Mexico City and two in rural communities in the state of Oaxaca. In each setting, one focus group included women with at least one previous Pap test, and one focus group included women who had never had the test. The authors found that barriers to the Pap test included lack of knowledge about cervical cancer etiology, unawareness of the Pap test , the perception that cancer is an inevitably fatal disease, problems in client-provider relationships, giving priority to unmet needs related to extreme poverty, opposition by male sexual partners, rejection of the pelvic examination, long waits for sample collection and results, and perceived high costs for care. Based on these findings, the authors recommend that more information be given to women in an effort to create "a culture of prevention" that incorporates use of the early detection program for cervical-uterine cancer. They recommend that the campaign include information about age at which testing should begin and end, time lapse between tests, instructions for preparing for the sample, a description of the procedure for taking the sample, instructions about when and where to return for the results, and basic etiology of cervical cancer. They also suggest that multiple communication strategies be used to promote the use of the Pap test, including promotion during contacts between health personnel and women; distribution of information by radio, posters, and pamphlets; promotion through community groups; and incorporating promotion of cervical cancer prevention into existing health programs.

Lazcano-Ponce, E.C. et al. **The cervical cancer screening program in Mexico: problems with access and coverage.** *Cancer Causes Control* 8(5):698–704 (September 1997).
The goal of this cross-sectional study was to determine the main factors for predicting participation in Cervical Cytology Screening Programs in populations with high mortality due to cervical cancer. A total of 4,208 women aged between 15 and 49 years from Oaxaca State (rural area) and Mexico City (urban area) were randomly selected through a national household-sample frame. The authors found that knowledge of what the Pap smear test is used for strongly predisposes use of screening programs in Oaxaca State and Mexico City. Other predicting factors included high socioeconomic level, high education level, and access to social security. The authors confirmed low coverage of the screening programs as an important problem in Mexico.

Mauad, E.C. et al. **Prevention of cervical cancer in a poor population in Brazil.** *Family Practice* 19(2):189–192 (2002).
The authors of this study assessed and implemented strategies to increase women's participation in cervical cancer screening among a poor population in Brazil. Their activities included interviewing the program coordinator during a popular radio show, broadcasting announcements in the targeted neighborhoods by using a loudspeaker, and home visits by nurses to discuss the screening service and distribute printed materials. Their program offered flexible hours, including evenings and weekends when necessary. For women who were having difficulty making it to the nearest health center, screening services were offered to them in their home using a gynecological table that could easily be transported. Using this strategy, the study achieved coverage of 75 percent of the target population: 1,044 out of 1,384 women interviewed underwent Pap test screening. Of these, approximately 95 percent used the closest health center and approximately 5 percent were screened in their home using the portable table.

Marcus, A.C. and Crane, L.A. **A review of cervical cancer screening intervention research: implications for public health programs and future research.** *Preventative Medicine* 27:13–31 (1998).
This article provides an overview of the published literature regarding intervention strategies for promoting cervical cancer screening and reducing loss to follow-up among women with abnormal smears. The authors found that mass media campaigns have had varying effects. These campaigns may work best when multiple media are used, when they promote specific screening programs that eliminate or reduce barriers for women, or when they are used in combination

with other strategies. The authors also note many positive examples of using outreach staff to promote cervical cancer screening. Mobile exam rooms also have been successful. Personalized letters to patient populations have been found to be effective, however mass or bulk mailings have not yielded impressive results. Several effective strategies were identified to reduce loss to follow-up, including multiple follow-up contacts, educational mail-outs, audiovisual programs, on-site educational presentations, transportation incentives, and economic vouchers.

Marrett, L.D. et al. **A proposal for cervical screening information systems in developing countries.** *International Journal of Cancer* 102:293–299 (2002).
In March 2001 a group of international experts came together with the Pan American Health Organization (PAHO) to discuss a framework and model for meeting the information systems needs of developing countries with respect to organized cervical cancer screening programs. This article summarizes the discussions and recommendations from the meeting. The proposed system would be modular in design to meet the needs and resources of developing countries, and would allow modules and data to be phased in as the system advances. Modules correspond to the need for "data capture," "database structure and management," and "required output." Issues that necessitate further dialogue include the need for a population register, the adequacy of the model, practicality of model, and legal issues concerning access to data.

Masood, S. **A plea for worldwide volunteer cervical cancer education and awareness program. A proposal from the International Academy of Cytology Committee on Cancer Detection for Medically Underserved Women.** *Journal of Clinical Cytology and Cytopathology* 43(4):539–543 (July–August 1999).
This editorial provides a brief review of the problem of cervical cancer and discusses the reasons why women still die from cervical cancer. The author suggests that lack of effective screening programs, especially for medically underserved women, and the continued dilemmas surrounding the practice of the cervical cytology screening test (that is, the Pap test) are the two main reasons for the medical community's failure to eradicate cervical cancer. Recommendations and strategies for overcoming these problems also are discussed. The author recommends that effective screening programs must integrate education and accessibility to health care services for all women regardless of age, race, ethnic background, and socioeconomic status. It is essential to reach women, educate them, and screening tests and responsive health care facilities. Integration of educational programs, Pap testing, and other diagnostic methods such as colposcopy in a mobile clinic is one innovative way of persuading women to utilize cancer prevention programs.

PATH (Program for Appropriate Technology in Health). **Assessing Health Need/ Community Demand for Cervical Cancer Control: Results From a Study in Kenya.** *Reproductive Health Reports* 1 (December 1996).
This report summarizes the purposes of a tool to assess the health need and community demand for cervical cancer services and results generated by use of the tool in two Kenyan sites. It also includes a complete reproduction of the tool, including questionnaires used in interviewing health care providers and prospective cervical cancer service clients about cervical and cancer and other related health services.

Strickland, C.J. et al. **Walking the journey of womanhood: Yakima Indian women and Papanicolaou (Pap) test screening.** *Public Health Nursing* 13(2):141–150 (April 1996).
The goal of this study was to examine the understanding of Pap testing among Yakima Indian women of eastern Washington to support the community in the design of effective cervical cancer screening interventions. Using the Grounded Theory research methodology, the authors analyzed data collected from 15 interviews, focus groups, and participant observation. A major theme from the finding was "walking the journey of womanhood," which included four phases: starting the journey, blooming, heading the household, and becoming an elder. The authors confirmed previous findings that the issues of structure of care, provider-patient communications, and community education for the women must be addressed if Pap test-screening interventions for the Yakima women are to be effective. Education needs to target women heading the households and elders as they have a great influence on the younger women. Messages need to be wellness and community oriented. The authors emphasized the use of traditional methods of education, such as storytelling, talking circles, and role modeling.

Tatum, C., et al. **Development and implementation of outreach strategies for breast and cervical cancer prevention among African American women.** *Journal of Cancer Education* 12(1):43–50 (1997).

This study was designed to test the effectiveness of clinical and community outreach to improve screening rates among low-income, minority women in the United States, particularly women living in subsidized housing communities, age 40 and over. The project used five strategies to reach and influence the target population: (1) education on women's issues that included cervical and breast cancer prevention; (2) media campaigns; (3) inclusion of religious ideals and beliefs in educational classes and community outreach; (4) the use of information centers to distribute materials; and (5) a community-wide cancer awareness event. Preliminary findings indicated that maintaining uninterrupted access to the target population was critical to successful community efforts. In addition, the authors found that developing good rapport with community leaders was vital. Convenient scheduling, small incentives, and refreshments were strongly related to the degree of women's participation in the meetings. Successful education materials were those packaged in simple, logical terms, and classes emphasized participation over didactic presentations.

Top of page

Key resource documents

Miller, A.B. ***Cervical Cancer Screening Programmes: Managerial Guidelines.*** Geneva: World Health Organization (1992).
These guidelines outline management issues that must be considered when setting up a cytology screening program. After reviewing the natural history of cervical cancer, the guidelines detail strategies for: deciding whether to initiate cervical cancer screening; health service sectors through which screening can be offered; issues related to age of initiation and frequency of screening, health education needs; monitoring and evaluation needs; and other areas. The guidelines then provide specific strategies for providing cervical screening in primary health care settings and outline issues surrounding information systems for cervical screening, including the goals, characteristics, and data requirements of information systems. Lastly, the guidelines describe an approach to reducing cervical cancer mortality in countries where cytological screening cannot be provided. This approach, called downstaging, focuses on detecting early cancer when it is still treatable.

PAHO (Pan American Health Organization). **Cancer of the uterine cervix.** *Bulletin of the Pan American Health Organization* (special issue) 30(4) (December 1996). (Available in English and Spanish.)
This special issue of the PAHO Bulletin includes 11 reviews and research articles on cervical cancer in the Latin American and Caribbean region. The articles include information on the epidemiology of cervical cancer in the region, the effectiveness of Pap testing in several countries, and women's knowledge and concerns about Pap testing in Chile and Mexico. Short communications on specific program activities and reports from the field also are included, as well as a list of recommended readings.

PAHO (Organización Panamericana de la Salud). **Manual de normas y procedimientos para el control del cancer de cuello uterino.** Organización Panamericana de la Salud, Serie PALTEX Para Ejecutores de Programas de Salud, No. 6, Washington, DC (1990).
This Spanish-language PAHO publication reviews key managerial and technical aspects regarding cervical cancer control, with an emphasis on norms and procedures appropriate for the Latin American and Caribbean setting. The document includes sections that describe basic considerations for cervical cancer control, guidelines for cytological screening, diagnostic and treatment procedures, management of an effective program, and program monitoring and evaluation. The publication also includes several useful appendices that illustrate specific equipment and supply needs, evaluation indicators for cervical cancer control programs, and clinic and cytology registry forms.

PATH. ***Planning Appropriate Cervical Cancer Prevention Programs.*** 2nd Edition Seattle: PATH (2001). Available online at http://path.org/files/cxca-planning-appro-prog-guide.pdf. PATH/PAHO edition available in Spanish (www.path.org/resources/cxca_publications.htm).
This revised edition of *Planning Appropriate Cervical Cancer Prevention Programs, 2nd Edition,* is designed for program managers, policy makers, and advocates working to launch or strengthen cervical cancer prevention efforts in their communities. The guide provides a global overview of the magnitude of the problem and outlines key

recommendations for program managers and policy makers to consider as they design cervical cancer control programs. The guide summarizes recent research, profiles program experiences, and presents analyses related to cervical cancer control, with a specific focus on program and policy implications and emphazing considerations for planning programs in low-resource settings.

World Health Organization (WHO). **Cytological screening in the control of cervical cancer: technical guidelines.** Geneva: WHO (1988).
These guidelines were designed to be used in conjunction with the WHO managerial guidelines abstracted above (Miller 1992). After a general introduction to the problem of cervical cancer and the role of cervical cytology in cervical cancer control, the guidelines provided detailed information on collection of cervical smears; cytology laboratory processes; diagnostic, treatment, and follow-up procedures; monitoring and evaluation issues; and personnel, equipment, and supply needs. One section of the guidelines also outlines common faults of screening programs and suggested solutions.

WHO. **Cancer pain relief and palliative care: report of a WHO expert committee.** Technical Report Series 804. Geneva: WHO. (1990).
This report summarizes the findings of a meeting of the WHO Expert Committee on Cancer Pain Relief and Active Supportive Care. The report reviews the principles of palliative care, including obstacles to implementing effective palliative care. It defines the type of pain associated with cancer, as well as other symptoms associated with advanced cancer, and describes the drugs used to treat cancer pain. The report emphasizes that palliative care must encompass the psychosocial and spiritual needs of cancer patients and discusses ethical issues that providers may need to consider when working with terminally ill people. Lastly, the report lists key program issues that must be considered before implementing palliative care (including education and training needs) and includes recommendations to WHO and WHO member-states on key strategies for making palliative care accessible to those who need it.

World Health Organization (WHO). ***Cancer Pain Relief.*** **2nd ed. (with a guide to opioid availability).** Geneva: WHO (1996)
This document updates the 1990 WHO report summarized above. In particular, opioid availability is addressed, including strategies for overcoming barriers to obtaining a regular supply of opioids.

Top of page

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
- Spanish Edition

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PATH

Program Examples

The cervical cancer programs in developing countries listed below illustrate some of the strategies developed to overcome obstacles and what has been learned from program experience.

Submit your own program example.

- Chile: Challenges and lessons learned from a cervical cancer screening and treatment program.
- Colombia: Challenges and lessons learned from a nationwide cervical cancer control program.
- Costa Rica: Research project investigating the role of HPV infection and its cofactors in the etiology of high-grade cervical neoplasia.
- India: A cervical cancer screening project effectively using a network of community resources.
- Kenya: Barriers and successes encountered in a cervical cancer control project.
- South Africa: Challenges to a nationwide screening project and recommendations to improve cervical cancer screening.
- Thailand: Using mobile units to improve cervical cancer screening among rural women.
- Vietnam: Assessing the cost-effectiveness of a five-year interval Pap screening program.

Top of page

Chile

Cervical cancer is one of the leading causes of mortality in women over 35. Individuals in Chile began working toward a cervical cancer screening, diagnosis, and treatment program in the 1960s; only in the past decade, however, has a coordinated program with monitoring and evaluation been implemented. Having data to show the impact of services has helped the cervical cancer prevention program win official recognition and greater government support.

The major challenges identified by the Chilean program were:

- retaining highly motivated and trained professionals in the program;
- keeping resources focused on high-risk groups;
- improving registration of pre-invasive and invasive cancer;
- allocating adequate resources for community work, mass media, and cytology labs to continue increasing coverage;
- overcoming cultural barriers to Pap smears;
- including private labs in the cytology quality control program; and
- integrating services with other women's health promotion programs.

Lessons Learned

- All screening programs should follow the principles of public health interventions from the beginning. It took 20 years to realize that the cervical cancer screening program in Chile was having little effect, and another 8 years to convince the majority of health care professionals that new strategies were research-based and cost-effective.
- Success breeds success. Better coordination and guidelines, improved quality control, and more focused screening have helped the program optimize resources and become successful. As the program has shown improved results, the government has been more willing to provide administrative and financial support.

For more information, please contact:
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Top of page

Colombia

Colombia is in the midst of an epidemiological transition, and many aspects of women's health are improving markedly. Yet cervical cancer remains a serious health problem throughout the country, despite efforts to make screening more widely accessible.

The Colombian public health system, private organizations such as PROFAMILIA (a family planning nongovernmental organization), and the Colombian National League Against Cancer have been offering Pap smears since the mid-1970s. In 1990, after earlier efforts failed to show a significant impact on cervical cancer morbidity and mortality, a five-year, nationwide cervical cancer control program was initiated with the goal of reducing the incidence of invasive cervical cancer by 25 percent. The three main program objectives were to:

- To provide Pap smears to 60 to 90 percent of women aged 25 to 69 within a three-year period, with special emphasis on reaching women of low socioeconomic status.
- To provide follow-up to 90 percent of all women obtaining Pap smears through the program.
- To establish reference centers for diagnosis and treatment of women with precancerous lesions.

The major challenges of Colombia's cervical cancer control program were:

- Expanding cervical cancer screening to women beyond their childbearing years. (The health system traditionally has offered cervical cancer screening primarily to women during their peak childbearing years, which, in Colombia, is before age 35.)
- Training enough cytologists to meet program demand. (There continues to be a shortage of trained cytotechnicians, particularly in certain parts of the country. Pressure from the medical pathologists association

for a mandatory four-year training program in cytotechnology has complicated efforts to train more cytotechs quickly.)
- Improving quality of care, particularly in terms of treating women with respect and paying attention to their concerns. (Efforts are underway to integrate quality-of-care issues into all program components.)
- Developing an effective information system so that the impact of the program on Pap smear coverage and, ultimately, mortality and morbidity can be evaluated.

Lessons Learned

- Bottlenecks to program implementation should be identified at the start. In the Colombian program, the shortage of cytotechnicians was a key barrier to meeting program needs. In addition, the growing demand from women asking for Pap smears put pressure on the system to train more cytologists. In most countries, developing systems to ensure the growing availability of cytotechs is a key program need.
- It is crucial to develop an effective information system that allows for regular evaluation of program activities and achievements. This evaluation allows for identification of both program successes and program activities that need to be improved.
- Women living in poorer, less accessible areas often are at highest risk for cervical cancer. Special strategies must be devised to reach these women. In Colombia, strategies such as special "cytology days" in shanty towns have been initiated using radio, megaphones, and church calls to encourage women to attend.
- It is important to remember that the challenges of offering effective cervical cancer screening, diagnostic, and treatment services are not primarily technical challenges, but rather social and cultural ones. Cultural issues in local communities and in the medical/health communities can influence program success. Dr. Margarita Ronderos Torres concludes that "working together, respecting each other to deliver technology safely, efficiently, and effectively, is probably the key to success."

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Top of page

Costa Rica

Guanacaste is a rural province in northwest Costa Rica. Guanacaste has reported consistently high rates of invasive cervical cancer, despite the existence of a national cervical cancer screening and treatment program. During the five-year period from 1988 to 1992, incidence rates of invasive cervical cancer ranged from 23.5 to 45.1 per 100,000 women. This is higher than average in Costa Rica and at least four times higher than comparable rates in the United States. The main difference between high and low-incidence areas in Costa Rica may be related more to varying prevalence of risk factors than to the intensity of screening.

In an attempt to better understand why cervical cancer incidence in Guanacaste has remained high despite the availability of screening and treatment, the Costa Rican Foundation for Education in Medical Sciences—a part of the CCSS—is implementing a six-year study in the province to investigate the role of HPV infection and its co-factors in the etiology of high-grade cervical neoplasia, and also to evaluate new cervical cancer screening technologies. This study is being carried out in collaboration with (and with funding from) the U.S. National Cancer Institute.

The major challenges encountered during this research project were:

- Limited experience of investigators and administrators with regard to contract negotiation and management.

- The high cost of maintaining the number of full-time staff necessary to achieving high follow-up rates.
- Ensuring standard protocols for colposcopic evaluation and pathologic evaluation of specimens.
- Limited expertise in procuring equipment and materials from the United States, which has led to unexpected delays and additional expense.

The preliminary findings from this study are that:

- It is possible to achieve high participation in cervical cancer screening programs and necessary follow-up through personal attention to patients, flexible clinic schedules, and allocation of resources for follow-up. (Participation rates have been above 93 percent for all components of the study including interviews, exams, and biological sample collection.)
- Several new screening techniques are available, which may enhance the impact of cervical cancer prevention programs in developing countries. Until their cost is reduced, however, these new technologies may not be affordable to nonresearch programs.

For more information, please contact:
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Top of page

India

Editor's Note: The cervical cancer screening strategy implemented in the program example below involves simply looking at the cervix for signs of cervical cancer. This strategy, also known as "downstaging," attempts to identify cervical cancer at an earlier, more treatable stage. (Stage I means that the carcinoma is confined to the cervix, stage II means the carcinoma extends beyond the cervix, but has not extended to the pelvic wall, stage III means the tumor involves the lower third of the vagina or has extended to the pelvic wall, and stage IV means the carcinoma has extended beyond the true pelvis. For a more detailed description of cervical staging, see the NIH Consensus Statement on Cervical Cancer (http://odp.od.nih.gov/consensus/cons/102/102_statement.htm.) Other investigators who have evaluated the use of downstaging in detecting cervical cancer have concluded that it is not a useful procedure for cervical cancer control (Nene et al. 1996). Nonetheless, this example illustrates an effective use of a network of community resources to promote a cervical cancer program.

Cervical cancer is the most common cancer among women in India, with approximately 71,600 new cases occurring each year. In 1985, staff of the Department of Gynaecologic Oncology at the Kidwai Memorial Institute of Oncology initiated an effort to develop an appropriate strategy of the control of cervical cancer in India.

Phase I of the project started in 1991 and involved two studies to assess the feasibility of using the existing public health infrastructure to downstage cervical cancer. The goal of the study was to determine the effectiveness of female health personnel in communicating health information, performing visual inspection, and in triaging cervical abnormalities. Women who were identified with a cervical abnormality were referred to the institute, where they received appropriate treatment for visible lesions and further investigations (including Pap smear and colposcopy) if no lesion was visible. The study found that health workers in primary health centers could perform visual inspection of the cervix, but that the additional responsibility of raising awareness about cervical cancer and encouraging local women to visit the health center for screening was more than the health personnel could handle. They noted that the success of the intervention depended a great deal on having a female provider at the primary health center who was interested in the project and willing to put effort into its implementation. They also found that many women needed the consent of their husbands or mothers-in-law to have a health test, suggesting a need for more active education of men and family members about the

importance of cervical cancer screening.

In phase II of the project, two nongovernmental organizations, PRAXIS and ADATS, collaborated with the institute to develop a broad-based collaborative approach to cervical cancer screening. The two organizations disseminated information about cervical cancer and encouraged women to seek cervical screening by trained health workers. This approach allowed more women to be recruited for screening and enabled primary care staff to screen larger numbers of women than in the earlier study.

A recent component involved an assessment of awareness about early detection of cervical cancer among urban underprivileged women. A Knowledge, Attitudes, and Practices Survey was administered to a representative sample of women fitting this description. Over 80 percent of the women were not aware of cancer and more than 99 percent had never heard of a test for cancer. Some 70 percent stated that they would be interested in undergoing such a test, however. This component of the project also involved implementation of an early detection program for cervical cancer in an urban setting, but there is no record of the accuracy of the examination or the analysis of women's compliance in seeking testing or being referred for treatment.

Lessons Learned

- Success of the intervention depended on having a female medical officer at each site interested in the project.
- The responsibility of creating a demand for services should not be placed solely on the health workers.
- More empowerment of women and more education for men is necessary for large numbers of women to be able to receive health treatment.

Some of the future plans for new and continued activities in this program in India are:

- Promoting collaborations between the Kidwai Institute and additional organizations to promote early detection of cervical cancer.
- Recruitment of private institutions, hospitals, or local gynecologists interested in providing referral services for the project.
- Involving female "panchayat" members to impart health education messages and to ensure that primary health centers provide cervical cancer services to women.

For more information, please contact:
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Top of page

Kenya

The limited data available suggest that cervical cancer is a serious problem in Kenya. Hospital-based registries indicate that the disease accounted for 8 to 20 percent of all cancer cases from 1981 to 1990. At Kenyatta National Hospital in Nairobi, which has the country's only radiotherapy unit, more than 500 cases are referred for treatment every year. Since many women are unable to travel to Nairobi from other parts of the country for diagnosis and treatment, this figure likely represents a very small proportion of the total number of women in need of care. In fact, limited research suggests that over 600,000 women throughout Kenya may have cervical dysplasia, a significant portion of whom may have high-grade or severe dysplasia, thus requiring treatment to prevent cancer from developing.

In 1992, the Kenya Medical Women's Association (KMWA) initiated the Well-Woman Clinic in Nairobi, in collaboration with the Family Planning Association of Kenya, to provide a variety of interventions to improve women's health. The first intervention that was introduced was cervical cancer screening. In 1994, KMWA established its own facility to support the expansion of cervical cancer and other services. A baseline study was conducted during the first phase of the project (May through December 1994) in which 520 women were screened. Of these women, about 2.9 percent had atypia, 5.4 percent had CIN I, 3.3 percent had CIN II, 2.3 percent had CIN III, and 0.5 percent were diagnosed with cancer.

Major barriers encountered by KMWA in establishing a cervical cancer control program include:

- A national health policy that does not directly address cervical cancer as a priority, which in turn lessens the emphasis on cervical cancer in medical education programs.
- Inadequate provision of equipment and supplies for screening in public health clinics.
- Lack of accurate incidence and prevalence data for planning.
- Misinformation about the disease on the part of women and health care providers.
- Poverty, which makes health care inaccessible to many women.

Although limited in scope, KMWA's efforts have been successful largely because of the following:

- Screening and treatment are kept affordable because KMWA members (gynecologists and pathologists) offer their consultation services for free.
- Referral of cancer cases to either public or private hospitals for management is arranged through the network of KMWA members working in these facilities. As a result, women who need follow-up receive it quickly and easily.
- Research activities have funded the training of KMWA gynecologists to perform colposcopy, as well as to become trainers themselves. Training for nurses in taking Pap smears also has been conducted.
- Functioning networks with other organizations to share resources, materials, and technical skills have allowed the program to reach more women.

For more information, please contact:
Dr. Lucy Muchiri, Coordinator, WWC and Secretary, KMWA Council, Kenya Medical Women's Association, Kodi Road, PO Box 49887, Nairobi, Kenya
Telephone: 254-2-506-287; Fax: 254-2-503-239

Top of page

South Africa

Cervical cancer is the most common cancer among women in South Africa and accounts for about 25 percent of cancer deaths among black South African women. Death rates among women being treated for cervical cancer vary by race and geographic location. Though data are sketchy, information from Cape Town suggests that the peak incidence of dysplasia occurs among women in the 29 to 39 age group. A cervical cancer screening research project in Soweto (an urban township) revealed extremely high rates of CIN and invasive cancer in women aged 40 to 60, and unexpectedly high rates of dysplasia among teenagers.

South Africa has not had great success to date in implementing effective cervical cancer screening efforts. In the 1970s, the Department of Health advocated that Pap smears be done only if the cervix looked abnormal, a policy that was abandoned because, in general, by the time a clinician notices growths or discharge, cancer is already advanced. In the 1980s, the availability of Pap screening services was further curtailed as cervical cancer deaths were decreed to be less serious than other health challenges. In 1989, a policy to screen women once in their lifetime at age 40 was initiated, but

no coordinated mechanism to implement the policy was developed. Therefore, services remain variable. Although screening is theoretically available at Ob/Gyn, family planning, and ante- and postnatal clinics, little routine screening occurs in the public sector. In general, women have to initiate screening by specifically requesting a Pap smear.

As a first step toward developing a rational plan for promoting and implementing a national cervical cancer screening program, researchers from the Women's Health Project at the Center for Health Policy, Department of Community Health at the University of Witwatersrand Medical School in Johannesburg, reviewed the cost-effectiveness of various screening assumptions, including screening interval. A summary of these findings was presented in a policy paper entitled *Toward a National Screening Policy for Cancer of the Cervix in South Africa.* This document concludes that the current practice of opportunistic screening and treatment of precancerous and cancerous lesions is not a rational use of resources. A policy aimed at screening either 100 percent or 60 percent of all women over age 20 every five years would be at least as cost-effective as the current policy of treatment without an organized screening program. Another important finding is that use of specialists to perform Pap smears is not a practical or cost-effective approach.

Some of the major challenges to developing a national screening program in South Africa that have been identified are:

- Education of women: Any policy to increase screening should include an education program.
- Integrating services: Any planned screening program should be integrated into the existing clinic system.

Some of the key recommendations for cervical cancer programs in South Africa are applicable to most programs working to improve cervical cancer control:

- Increase the number of women having Pap smears (coverage) rather than focusing on more frequent screenings.
- Develop effective quality-control systems in obtaining and interpreting Pap smears.
- Ensure appropriate follow-up of abnormal smears.
- Ensure that Pap smear services are effectively integrated into the existing health care infrastructure.
- Train providers to improve sensitivity toward client issues and concerns.

For more information, please contact:
Dr. Sharon Fonn or Ms. Barbara Klugman, Women's Health Project, c/o SAIMR, P.O. Box 1038, Johannesburg 2000, South Africa
Telephone: 27-11-489-9917; Fax: 27-11-489-9922

Top of page

Thailand

Cervical cancer is the most common type of cancer among women in Thailand. In the early 1990s, a mobile unit program was developed in the Mae Sot District, Tak Province, to improve screening coverage and knowledge of cervical cancer among rural Thai women.

Since the 1970s, cervical cancer screening in the Mae Sot District hospital has been performed mainly through the maternal and child health/family planning services. A one-week mass screening campaign in which women can receive a Pap smear at no charge has been conducted in the hospital since 1986. Despite the availability of these services, a 1991 survey of women aged 18 to 65 revealed that only 21 percent knew about the Pap test, and only 20 percent had ever been screened.

In order to improve screening coverage in rural Thailand and to increase awareness of cervical cancer, a mobile unit program was established in 1993. Supported by the Provincial Health Office, the mobile screening unit targeted women

between the ages of 25 and 60. Mobile unit activities included providing education, asking health center workers and trained village health communicators to invite women personally to the screening program, and collecting Pap smears throughout all 54 rural villages in the district. Pap smears were provided free of charge and were obtained by trained public health nurses under the supervision of the project physician at the health center or the village primary school in each village. All Pap slides were sent to the cytology laboratory at the hospital. After the first campaign was conducted in January and February 1993, another campaign was implemented in 1996.

To evaluate the program's effect on knowledge and use of cervical cancer screening, the results of three interview surveys of women aged 18 to 65 were compared. The first survey was completed in January 1991, before the program had been established; the second was completed in January 1994, one year after the first screening campaign; and the third was completed in January 1997, one year after the second campaign. Survey results include:

- The percentage of women who could identify cervical cancer as the most common cancer in women rose from 31 percent in 1991 to 66 percent in 1994 and 69 percent in 1997.
- The belief that women can have asymptomatic cervical cancer increased from 20 percent in 1991 to 53 percent in 1993 and 64 percent in 1997.
- The proportion of women who knew about the Pap test rose from 21 percent in 1991 to 57 percent in 1994 and 76 percent in 1997.
- Of the women who knew about the Pap smear, the proportion who understood that it could detect asymptomatic cervical cancer grew from 78 percent in 1991 to 92 percent in 1993 and remained at 92 percent in 1997.
- The proportion of women who had ever had a Pap test increased from 20 percent in 1991 to 58 percent in 1994 and 70 percent in 1997.
- The mobile unit screening program became the most commonly reported service for Pap screening among rural Thai women.
- The mobile unit effectively targeted older women. More smears of women older than 25 and particularly women older than 45 were taken by the mobile unit than by the other screening services.
- The mobile unit accounted for 85 percent of all cervical intraepithelial neoplasia (CIN) III and all invasive cancer identified among the Pap smears examined in the district from 1992 to 1996.

Lessons Learned

- Health education, personal invitation, and smear-taking activity are crucial components of cervical cancer screening programs.
- A mobile unit program may provide effective screening for early detection of cervical cancer among women in rural areas where existing screening services cannot reach at-risk female populations (particularly older populations).

For more information, please contact:
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Telephone: 66-55-531229; Fax: 66-55-533046

Information adapted from Swaddiwudhipong, W. et al. A mobile unit: an effective service for cervical cancer screening among rural Thai women. *International Journal of Epidemiology* 28:35–39 (1999).

Top of page

Vietnam

Cervical cancer is the leading cause of cancer-related death among women in the Socialist Republic of Vietnam. Until recently, Vietnam was one of many developing countries in which Pap smear screening programs were virtually

nonexistent. The absence of Pap screening programs in developing countries such as Vietnam is due in part to the belief that costs to implement such programs would be prohibitively expensive. The cost-effectiveness of implementing conventional Pap screening in a developing country had never before been formally examined. This summary describes the results from a study of the cost-effectiveness of a five-year interval Pap screening program in Vietnam, assessed from a societal perspective using decision analytic methods.

The Viet/American Cervical Cancer Prevention Project, initiated in 1993 by physicians in Vietnam and the United States, supports the development of a comprehensive, cost-effective cervical cancer prevention program in Vietnam. The organization completed a cost-effectiveness analysis in 1999 that estimated that building a nationwide Pap screening program in Vietnam (based on five-year intervals between screenings) would average less than US$150,000 (1999 constant-value) annually during the ten years assumed necessary to develop the program. This figure includes costs for salaries, disposable supplies, equipment, clinic space, laboratory space, and overhead related to Pap smear screening and preventive treatment. It does not include costs of training by international consultants for community mobilization, cytology, or treatment. The estimate also excludes costs associated with the treatment and care of women with invasive cervical cancer. (Women in Vietnam with invasive cervical cancer currently are treated with surgery and radiation therapy.)

Annual program-maintenance costs were estimated to average less than US$0.092 per woman in the target screening population (women 30 to 55 years of age), an amount that appears affordable for the 1999 average per-capita income of US$300. At this level of investment, the Viet/American Cervical Cancer Prevention Project estimated that cervical cancer incidence and mortality in Vietnam would be reduced by 37 percent with participation by 60 percent of women in the target screening population, and by 58 percent with participation of 100 percent of women in the target screening population. With 70 percent program participation, cost-effectiveness will be US$725 per DALY. Staffing requirements for the fully established nationwide program will include 292 Pap test collectors, 204 cytotechnologists, 133 secretaries, 35 pathologists, and 9 gynecologists. Budget and personnel requirements will be considerably lower if only high-risk geographic areas are targeted.

Based on the study results, the Viet/American Cervical Cancer Prevention Project instituted de novo population-based Pap screening in Ho Chi Minh City and in Hue. Pilot-scale Pap screening programs have been established in Hanoi and in Danang.

Program Challenges

Some of the challenges to developing a successful screening program in Vietnam include:

- developing effective community-outreach methods to maximize the level of participation among women in the target screening population;
- implementing and maintaining effective quality-control and quality-assurance programs, particularly in the centralized cytology laboratories;
- improving curative treatment services for women who are discovered to have invasive cervical cancer; and
- maintaining excellent working relationships among diverse groups and institutions in order to ensure the success of cervical cancer prevention efforts in Vietnam.

Implications for Other Programs

- The study results suggest that Pap smear screening programs can be developed in some settings, such as Vietnam, with a relatively low level of investment, assuming external assistance is available for training and technical assistance.
- While the effectiveness and cost of some alternatives to the conventional Pap test in developing countries are still being investigated, the results from the Vietnam cost analysis seem to suggest that the implementation of conventional Pap screening services in developing countries such as Vietnam could be inexpensive and cost-

effective.
- Results of a well-designed cost-effectiveness analysis can provide persuasive evidence that can help gain support for cervical cancer prevention activities.
- Training of non-physician providers to provide cytologic screening services is a cost-effective strategy.

Some of the most critical barriers to the expansion of cervical cancer prevention services in any country are social and political obstacles to organizing the coalitions needed to secure participation, and will remain so irrespective of the screening methodology eventually employed in any nation.

For more information, please contact:
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Top of page

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
- Spanish Edition

Note: **This site is designed to meet web standards and uses Cascading Style Sheets for layout and design. If you can read this note, you are either printing this page or browsing it with a client that does not support current Web Standards. Text content of this site is available to any web client, but to view, use, and enjoy this site to the fullest, please upgrade to a browser that supports web standards.**

Links

Updated August 6, 2004

Listed below are useful web resources and organizations experienced in cervical cancer control in low-resource settings.

Please note that PDF files require Adobe Acrobat Reader software, which can be downloaded for free at www.adobe.com/products/acrobat/readstep.html.

For general reproductive health links, go to the RH Resources page. The Conferences section includes information about upcoming events related to cervical cancer.

If you know of a resource to be included in this list, please send the URL (web address) and a description to: rho@path.org.

Information resources

Cancer Resources on the WEB from International Union Against Cancer
www3.uicc.org
A list of organizations, online journals, and networks involved in cancer prevention.

CANCERLIT from National Cancer Institute's International Cancer Information Center
www.cancer.gov/CancerInformation/cancerliterature
CANCERLIT is a bibliographic database containing more than 1.3 million citations and abstracts. These are drawn from

over 4,000 different sources including biomedical journals, proceedings, books, reports, and doctoral theses from 1963 to the present. CANCERLIT is updated with more than 8,000 records every month.

Cancer Mondial

www-dep.iarc.fr
An online source of information on global cancer incidence, mortality, and survival data compiled by the International Agency for Research on Cancer from national cancer registries. This site also contains information on manuals, software, and training opportunities for cancer researchers.

Cervical Cancer Email Discussion Group

www.path.org/resources/cxca_listserv.htm
PATH (Program for Appropriate Technology in Health) has established a cervical cancer email discussion group that allows individuals and groups worldwide to share information on issues pertaining to cervical cancer in low-resource settings. For more information, send an email to cxca@path.org.

Cytopathology Tutorial from University of Utah

www.medlib.med.utah.edu/WebPath/TUTORIAL/CYTOPATH/CYTOP ATH.html
Cervix pathology slides. To view this page, you will need web browser that can view images.

The HPV Test

www.thehpvtest.com
Although aimed at a U.S. audience, this website offers readers relevant information on cervical cancer and HPV, discusses uses and benefits of HPV testing, provides a glossary of terms, and lists links to other websites on HPV testing and cervical cancer. This website is supported by the Digene Corporation, manufacturer of the Hybrid Capture II (HC II) HPV test.

National Cervical Cancer Coalition

www.nccc-online.org
This cervical cancer website includes sections on Pap smears, insurance reimbursement, patient information and support, the latest technologies, and controversial issues. The site is primarily oriented toward a developed-country audience, but also contains broadly applicable and useful information.

National Cervical Cancer Public Education Campaign

www.cervicalcancercampaign.org
Sponsored by the American Medical Women's Association, the National Cervical Cancer Public Education Campaign is designed to provide women with information about HPV and cervical cancer, existing and new methods to detect the disease, and guidelines for discussing cervical cancer with their health care providers.

National HPV & Cervical Cancer Prevention Resource Center

www.ashastd.org/hpvccrc/index.html
This resource center, run by the American Social Health Association, provides fact sheets on HPV, information on support groups, and a toll-free hotline (for the United States) to answer questions about HPV. The hotline is open from 2 p.m. to 7 p.m. EST, Monday through Friday. The number is (877) HPV-5868.

OncoLink from the University of Pennsylvania Cancer Center

www.oncolink.com/index.cfm
The University of Pennsylvania Cancer Center's OncoLink website provides a range of information, including an overview of cervical cancer, summaries of recent U.S. meetings on cancer, and examples of provider and client information on Pap tests, colposcopy, and dysplasia treatment. The site is aimed at a U.S. audience, but much of the

material (in particular the client-oriented material) could be readily adapted for use in other settings.

PUBMED Search: Cervical Cancer in Low-resource Settings

This search has been predefined. It contains more than 1,500 of the latest citations and abstracts from the PUBMED database.

U.S. National Institutes of Health Consensus Statement on Cervical Cancer

http://odp.od.nih.gov/consensus/cons/102/102_statement.htm
This National Cancer Institute site provides the full text of a 1996 consensus statement on cervical cancer. The statement includes detailed information on the etiology of cervical cancer and strategies for strengthening cervical cancer control in the United States. Although aimed at a U.S. audience, this detailed and fully referenced synthesis was prepared by a group of recognized scientific experts and is a useful reference for anyone interested in learning more about cervical cancer.

Top of page

Organizations

Note: In cases where an organization has specific cervical cancer information on its website, we have provided the link. Other organizations active in cervical cancer are also listed, without links but with contact information.

Alliance for Cervical Cancer Prevention (ACCP)

www.alliance-cxca.org
The ACCP was launched in 1999 by AVSC International (now EngenderHealth), IARC (International Agency for Research on Cancer), JHPIEGO, PAHO (Pan American Health Organization), and PATH (Program for Appropriate Technology in Health). The five-year project supports programs to clarify, promote, and implement strategies for preventing cervical cancer in developing countries. The ACCP website contains information about the organizations who make up the alliance, links to online publications and cervical cancer resources, information on the Alliance Small Grants Program, and information about the Cervical Cancer List, an international email discussion group on cervical cancer prevention issues. This website is available in English, Spanish, and French.

EngenderHealth

www.engenderhealth.org
EngenderHealth (formerly AVSC International) is an international organization committed to making reproductive health services safe, available, and sustainable by providing technical assistance, training, and information, with a focus on practical solutions that improve services where resources are scarce. Since 1995 EngenderHealth has been conducting a collaborative project with Capetown University, Columbia University, and the Cancer Association of South Africa to evaluate four screening methods for the detection of cervical cancer among previously unscreened women age 35 to 60. The methods being studied are direct visual inspection of the cervix, HPV DNA testing, cervicography, and cytology. Women with abnormalities on any of the screening tests undergo colposcopy with cervical biopsy. The results of this study will eventually facilitate implementation of effective diagnosis and treatment services in low-resource settings. They also will provide guidance in avoiding over-treatment and ensuring that screening services offered are cost-effective. The Winter 1999 issue of *AVSC News*, which is published four times per year, was devoted to preventing cervical cancer. Contact: Karen Beattie at kbeattie@engenderhealth.org .

International Agency for Research on Cancer (IARC)

www.iarc.fr
IARC is an affiliated research center of the World Health Organization, and serves as the primary compiler of international statistics on cervical cancer incidence (based on reports from cancer registries around the world). IARC's

work related to cervical cancer includes both descriptive epidemiology and clinical epidemiology research. IARC staff have conducted international research studies on HPV prevalence and HPV as a causal agent of cervical cancer and currently are undertaking a cohort study of HPV and cervical cancer in Colombia. Other research has focused on identification of additional risk factors and on testing of various detection methods. The IARC Unit of Descriptive Epidemiology provides access to Cancer Mondial, which includes two major collections of online data: (1) cancer incidence, mortality, and survival data worldwide, and (2) resources for cancer researchers.

International Union Against Cancer Fellowship Program

http://fellows.uicc.org
The International Union Against Cancer's fellowship program provides opportunities for investigators, clinicians, registered nurses, cancer society staff, volunteers, and nonmedical professionals to participate in long-, medium-, or short-term training experience abroad. Information and applications are available on the UICC fellowship website.

JHPIEGO (a Johns Hopkins University Affiliate)

www.jhpiego.org
JHPIEGO's goal is to increase the availability of high-quality reproductive health services. Since 1989, JHPIEGO has been exploring the feasibility of several low-technology (and low-cost) alternative methods for cervical cancer screening. Prominent among these is visual inspection. JHPIEGO has several demonstration projects underway that use cryotherapy to treat precancerous lesions identified by nurses using visual inspection. It is expected that these studies will show that visual inspection done by well-trained nurses will allow the quick and easy identification of patients who are suitable for immediate treatment with cryotherapy and referral of those requiring more aggressive treatment.

JHPIEGO also offers information on cervical cancer through their reproductive health website, ReproLine (www.reproline.jhu.edu/english/3cc/3cc.htm). The site contains two cervical cancer workshop proceedings in HTML and PDF files:

- Alternatives to Cervical Cancer Screening and Treatment in Low-resource Settings: 1997 Cervical Cancer Workshop Highlights
  (www.reproline.jhu.edu/english/3cc/3wkshp97/ccpr1997.htm)
- Training Issues in Cervical Cancer in Low-Resource Settings: 2000 Cervical Cancer Workshop (Summary)
  (www.reproline.jhu.edu/english/3cc/3wkshp00/ccpr2000.htm).

The Pan American Health Organization (PAHO)

www.paho.org
PAHO's Non-Communicable Disease Division has established three priority areas of activity: cardiovascular disease, diabetes, and cervical cancer. They have sponsored regional meetings on cervical cancer and are working to develop at least two cervical cancer control demonstration projects in the Latin American region. Plans for one of these projects are underway in Mexico in collaboration with the National Institute of Public Health in Cuernavaca, the Mexican Secretariat of Health, IMSS, and PATH. For more information, contact: Sylvia Robles at roblessy@paho.org.

PATH (Program for Appropriate Technology in Health)

www.path.org/programs/p-wom/cervical_cancer.htm
The overall objective of PATH's work is to advance policies to improve cervical cancer prevention and control strategies in low-resource settings through information dissemination and targeted research. PATH has produced several documents and articles on cervical cancer prevention and control (www.path.org/materials-keycats.php?keycategory=cervical%20cancer) and moderates a cervical cancer email discussion group. PATH also researches specific questions about appropriate technologies, effective program approaches, and user/provider perspectives. PATH carries out its work in partnership with governmental, NGO, and international agencies, and works to maintain communication with groups involved in cervical cancer work worldwide to share experiences, challenges, and key results.

World Health Organization (WHO)

www.who.int

In past years, the Cancer and Palliative Care unit was involved in studies of "downstaging" (visual inspection to identify early cancer) in a wide range of developing countries. Participants in these studies formed a WHO Network on Cervical Cancer, which still exists. In 1998, however, the Reproductive Health Technical Support division at WHO added cervical cancer to its list of reproductive health priorities and is now taking the lead at WHO/Geneva in addressing this problem. Their program includes focusing on long-term strengthening of developing country, cervical cancer control programs, with particular emphasis on early detection and treatment of preinvasive cancer. In addition, as part of its advocacy efforts, WHO plans to disseminate information about the public health importance of cervical cancer, the need to invest in prevention programs, and ideas for feasible and cost-effective approaches.

Top of page

Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
- Spanish Edition

Note: **This site is designed to meet web standards and uses Cascading Style Sheets for layout and design. If you can read this note, you are either printing this page or browsing it with a client that does not support current Web Standards. Text content of this site is available to any web client, but to view, use, and enjoy this site to the fullest, please upgrade to a browser that supports web standards.**

Presentations

Alliance for Cervical Cancer Prevention (ACCP) Presentation Materials
www.alliance-cxca.org/english/publications.html#presentations
The ACCP has developed a set of presentation materials for advocacy purposes that can be adapted to meet users' needs. Presentation topics include screening methods, such as Pap smear, VIA, and VILI; research methods; answering women's frequently asked questions; and meeting women's needs. Materials are available in English, Spanish, and French and can be downloaded as PowerPoint or PDF files.

Planning Appropriate Cervical Cancer Control Programs (PATH 1997)
[View a PDF of the full planning document. PDF file requires Adobe Acrobat Reader.]
An overview of the issues involved in program planning. This PowerPoint presentation contains 15 slides. [Note: There are image files totaling 149K on this page. Download may be slow on some Internet connections.]

Cervical Cancer Screening Presentation Graphics
www.reproline.jhu.edu/english/3cc/3cxcapg/cxcapg.htm
ReproLine offers cervical cancer presentation graphics—including a slide show, full-size transparencies, and a PowerPoint 95 presentation—that can be used during training courses and lectures. ReproLine also offers a range of other cervical cancer resources at www.reproline.jhu.edu/english/3cc/3cc.htm.

Cervical Cancer Prevention

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Planning Appropriate Cervical Cancer Control Programs (PATH 1997)

If you would like a copy of the actual PowerPoint95 presentation, request "Cervical Cancer PowerPoint Presentation" from rho@path.org


Planning Appropriate Cervical
Cancer Control Programs

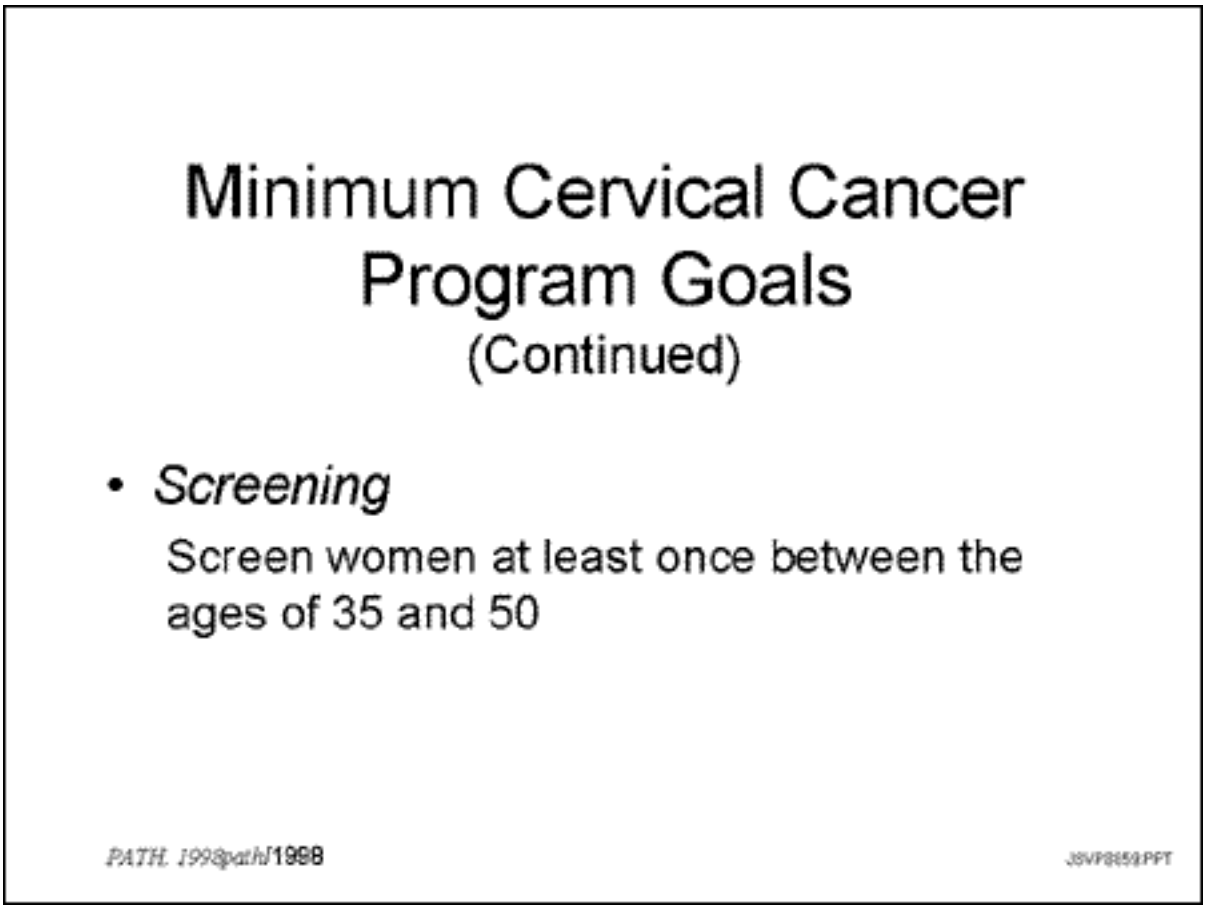
Assessing Health Need/ Community Demand

- Is problem big enough to warrant resources?
- Do clients/providers believe cervical cancer is a priority problem?
- Do clients/providers believe benefits of services outweigh disadvantages?

Minimum Cervical Cancer Program Goals

- *Information, Education, and Communication*

  Increase awareness of cervical cancer and available health services among women aged 35 to 50



Top of Page

Presentation:
Planning Appropriate Cervical Cancer Control Programs (PATH 1997)

Minimum Cervical Cancer Program Goals (Continued)

- *Diagnosis and Treatment*

  Treat women with high-grade dysplasia, refer those with invasive disease where possible, and provide palliative care for women with advanced cancer

Minimum Cervical Cancer Program Goals (Continued)

- *Monitoring and Evaluation*

  Collect service delivery statistics that will facilitate ongoing monitoring and evaluation of program activities and outputs

Key Inputs

- Proven IEC mechanisms
- Trained providers
- Adequate supplies and equipment
- Adequate cytology services
- Client follow-up capability
- Functioning referral network
- Effective information systems
- Palliative care options

"Bottlenecks to program implementation should be identified at the start. In the Colombian program, the shortage of cytotechnicians was a key barrier to meeting program needs. In addition, the growing demand from women asking for Pap smears put pressure on the system to train more cytologists."

Cost-effectiveness of Cervical Cancer Screening and Other Health Interventions

Intervention	Cost Per DALY* (US$)
Smoking cessation programs	20
Polio vaccination	20-40
STD management	1-55
Cervical cancer screening	100
Integrated antenatal/delivery care	30-250
Malaria treatment	200-500
Cervical cancer treatment/ palliative care	2600

*DALY = disability-adjusted life-year gained

Source; Jamison et al., 1993

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South Africa Cost Analysis

Screening oriented program

versus

Cancer treatment program

80% cost savings

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Two Screening Strategies in Chile

	Program 1	Program 2
Age	30-55 years	30-55 years
Screening frequency	3-yearly	10-yearly
Coverage	30%	90%
Mortality reduction	15%	44%
Cost per case detected	US$2,522	US$556

Source: Eddy, 1986, as described in Miller, 1992

Factors Affecting Cost-effectiveness of Cervical Cancer Control

- Existing health infrastructure
- Cervical dysplasia/cancer incidence
- Cervical dysplasia ⟶ cancer progression rate
- Availability of non-physician providers
- Invasive cancer management strategy

Factors Affecting Cost-effectiveness of Cervical Cancer Control (continued)

- Screening accuracy
- Cost of screening technology
- Screening frequency
- Treatment effectiveness
- Cost of treatment technology

*PATH. 1998*path*/1998*

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"Success breeds success. Better coordination and guidelines, improved quality control, and more focused screening have helped the program optimize resources and become successful. As the program has shown improved results, the government has been more willing to provide administrative and financial support."

*PATH. 1998*path*/1998*

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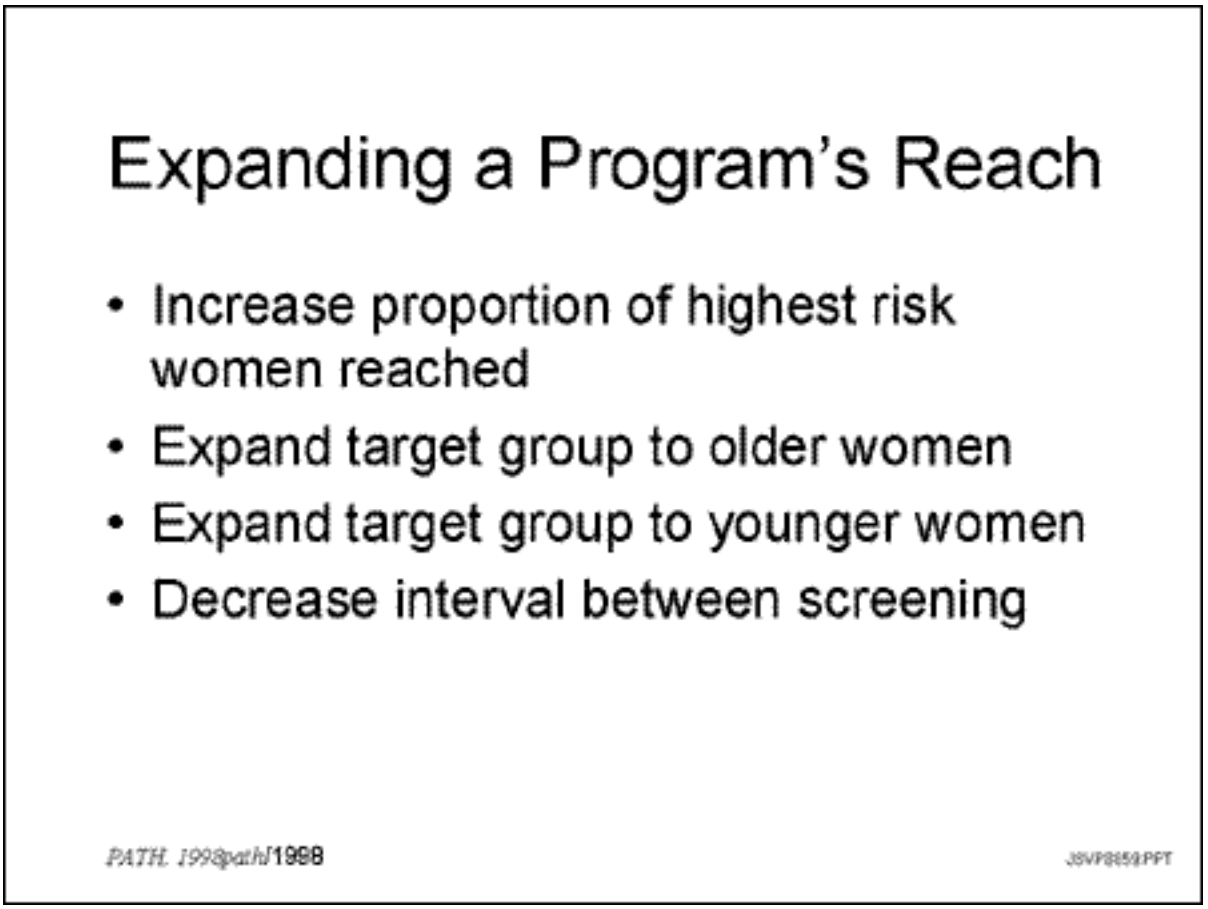

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Cervical Cancer Prevention

- Overview/Lessons Learned
- Key Issues
- Annotated Bibliography
- Program Examples
- Links
- Presentations
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