Cervical cancer is the third most common cancer worldwide and is the leading cause of death from cancer among women in many developing countries. In countries where regular cervical cancer screening is available, mortality due to cervical cancer has been reduced, but this has not been possible in developing countries where health-care systems lack the infrastructure, equipment and trained personnel to administer screening tests and sustain organized screening programs.

These are the key findings in a comprehensive policy analysis that, for the first time, uses formal analytic methods to synthesize data from several different studies on key components of the cervical cancer screening issue. Recently published in the Journal of the American Medical Association, the work should play a pivotal role in guiding decisions by national and international health organizations about how to combat this lethal but preventable disease that strikes women in their most productive years.

**Background**

Cervical cancer is caused by human papillomavirus (HPV), a sexually-transmitted virus, that infects the cells of the lower anogenital tract including the cervix. Cellular changes can be seen under a microscope and are classified as low-grade or high-grade squamous intraepithelial lesions. Most low-grade lesions, and a substantial proportion of those which are high-grade, will resolve on their own. A small percentage, however, will result in cancer over a 10 to 20-year period if not detected and treated.

For more information on HCRA visit our website at: www.hcra.harvard.edu
Cervical cancer screening programs in developed countries rely on the Papanicolaou (Pap) smear, a screening test that involves scraping cells from the cervix, fixing and staining them on a glass slide, and examining them under a microscope. This approach requires an established laboratory, highly-trained cytotechnologists, and up to three health care visits; one for screening, a second to evaluate abnormal screening tests using a procedure referred to as colposcopy, and a third to treat confirmed cervical precancerous lesions. In low-resource settings, such a strategy has proven difficult to implement and sustain.

Less complex strategies may offer more favorable options in low-resource settings. One approach uses simple visual screening methods, known also as direct visual inspection (DVI), in which the cervix is viewed after the application of an acetic acid (vinaegar) solution that causes precancerous cellular changes in the cervix to turn white. Mid-level health care providers (e.g., nurses) are trained to detect the abnormal lesions with the naked eye. An alternative screening method involves automated DNA identification of the cancer-causing strains of HPV in cervical samples, to identify women at high risk for cervical cancer. A third suggestion has been to couple these new screening approaches with treatment to be performed during the same visit, which eliminates colposcopy, the diagnostic confirmation step usually performed at the second visit. These approaches have all shown promise in large clinical studies conducted in low-resource settings.

These detection techniques compare favorably with Pap technology in terms of accuracy. Recent studies have found that Pap screens in the United States, where the training and equipment for this technology are fully developed, have a sensitivity of only approximately 50%. DVI and HPV-DNA perform as well as or better than Pap smear technology in detecting women with high-grade precancerous lesions. But compared with Pap technology, more women without cervical disease who are screened by DVI or HPV-DNA will have "false-positive" results. This means that a greater proportion of women without disease would receive treatment. The relative consequences to these women compared with the consequences in women with false-negative results (women screened by Pap, DVI, or HPV-DNA who have the disease but are not detected and therefore are not treated) need to be compared formally.

To determine whether these novel approaches will be clinically effective and cost-effective, we developed a comprehensive model to compare alternative screening strategies in developing countries. We used the model, together with country-specific data, to conduct a policy analysis comparing the clinical benefits and cost-effectiveness of different cervical cancer screening strategies in black South African women.

**About Policy Models and Economic Evaluation**

Mathematical models combine information from a wide range of parameters, allowing us to analyze more broadly and thoroughly the choices posed by a complex policy question. Inputs to public health models like this one include empirical information about the natural history of disease, the effectiveness and costs of various health interventions, along with demographic and epidemiological characteristics of the populations under study. By combining what we’ve learned from smaller studies of individual components of a problem, models let us examine the possible solutions more comprehensively.

Modeling also allows us to evaluate and compare multiple potential strategies. It allows us to compare choices *within* each strategy (e.g., whether it's best to screen every year, every three years, every five years, or only once in a lifetime; or whether it's better to treat a women immediately or have her come back for a second visit). Computer models allow us
to extrapolate costs and health effects beyond the time horizon of a single clinical study and can be used to identify which parameters have the greatest impact on outcomes (e.g., the age at which screening is done) to help focus future clinical research.

Mathematical models are often used to conduct cost-effectiveness analyses. The fundamental principle of a cost-effectiveness analysis is that choices will have to be made between alternative uses of resources. By providing estimates of not only health outcomes but also of costs, these analyses can help policy makers maximize public health within limited resources. A cost-effectiveness analysis produces an incremental cost-effectiveness ratio for each approach being evaluated (DVI vs. Pap vs. HPV). In this ratio, all-health outcomes (compared with the next best approach) are included in the denominator, and all costs or changes in resource use (compared with the next best approach) are included in the numerator. This type of analysis defines the opportunity cost of choosing one strategy over another.

**Analyzing the Cost Effectiveness of the Options**

A mathematical computer-based model was developed to simulate the natural history of cervical cancer in a cohort of previously unscreened 35-year-old South African women. The model is the first of its kind to incorporate the three health dimensions of HPV-DNA positivity, HIV infection, and cervical disease. South Africa was chosen because primary data were available on screening test performance, prevalence of HPV and cervical disease, prevalence of HIV, and costs. Data sources included a South African screening study, national surveys and fee schedules, and other published literature. Economic data included the cost of time spent traveling to and receiving screening, transportation, screening tests, complications from screening, treatment for precancerous lesions, and treatment for invasive cervical cancer.

Screening tests included DVI of the cervix, Pap smears, or testing for high-risk types of HPV DNA. Strategies differed by number of clinical visits, screening frequency, and response to a positive test result. Women with abnormal test results were treated with a simple outpatient procedure called cryotherapy, which destroys precancerous tissue.

**Findings**

Compared with no screening, a single lifetime screen using DVI with immediate cryosurgical treatment of women with abnormal results reduced the incidence of cervical cancer by 26%. The cost of this 1-visit screening/treatment strategy was so low compared with the benefits it provided that the total costs of the screening program were more than recouped by the savings to the health-care system that accrued from women not developing invasive cervical cancer.

The once in a lifetime screening using HPV-DNA testing followed by immediate treatment of abnormal test results (1-visit strategy) reduced the incidence of cancer even further, by 32%, and cost only $14(US) per year of life saved (YLS). HPV-DNA testing, followed by treatment of women with abnormal results at a second visit (2-visit strategy), reduced the incidence of cancer by 27% and cost $39 (US) per year of life saved (YLS).

1-visit strategies were always more effective and less costly than 2-visit or 3-visit strategies. In part this is because they eliminate the cost involved with the 2nd and 3rd visits, but more importantly they eliminate the loss to follow-up of women who don't return for a 2nd visit, which can be as high as 50% in resource-poor settings.
### Selected Strategies, Compared with No Screening

<table>
<thead>
<tr>
<th></th>
<th>% Reduction in Cervical Cancer Incidence</th>
<th>Cost-Effectiveness Ratio, (US $/YLS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One Visit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVI/cryosurgery</td>
<td>26</td>
<td>Cost Saving</td>
</tr>
<tr>
<td>HPV/cryosurgery</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td><strong>Two Visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVI, follow-up HPV</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>HPV</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Pap smear</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td><strong>Three Visits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pap smear</td>
<td>17</td>
<td>147</td>
</tr>
</tbody>
</table>

These 1-visit single-lifetime strategies resulted in cost-effectiveness ratios as good as or better than the health-care investments (e.g., childhood vaccination, mosquito nets to prevent malaria, and antiretroviral treatment of pregnant HIV-infected women to prevent transmission to the baby) that are currently affordable for developing nations.

Regardless of the screening method, screening women in very poor countries twice, three times, or five times in a lifetime added marginal life expectancy gains and significant additional cost. Using 1-visit DVI with immediate treatment, or 2-visit HPV testing, once in a woman’s lifetime, provided the best balance between clinical benefits and costs. For developing countries that are able to afford more than a single lifetime screening (e.g., $100 per YLS), screening twice in a lifetime with either of these strategies would increase the clinical benefits by approximately 50%.

The optimal age for screening, regardless of method, was between 35 and 40. This is the age at which the greatest percentage of the high-grade lesions that could lead to cancer begin to appear. Screening earlier or later is a less cost-effective use of resources. Some have argued that implementing a preventive screening strategy would be a poor use of resources in countries in sub-Saharan Africa where the average life expectancy has plummeted due to the AIDS epidemic. However, because we are targeting screening to women in their late 30’s and the peak incidence of HIV occurs more than a decade earlier, many of these women have avoided HIV-infection and have a relatively normal life expectancy. These women play an increasingly vital role as caregivers for children orphaned by the AIDS epidemic, and as educators in communities where many school teachers have died from AIDS.

### Discussion

These results add powerful information to the debate over how to combat cervical cancer in the developing world. They clearly support further clinical trials of these methods, some of which are already underway. But while cost-effectiveness analysis can help inform decision-making, it is only one input. Different methods may be more or less consistent with cultural norms in different countries. And different approaches require installation of different infrastructure and resources, each of which may be more or less suited to different nations. HPV technology, for example, requires installation of automated DNA testing equipment, supporting power supply equipment, and training of personnel to run such equipment.
Cryosurgery requires different equipment and training. Indeed, some of the up-front costs of establishing the requisite infrastructures were not incorporated into our analysis, since these costs are unknown and will likely be region and time-specific.

Cervical cancer screening is but one of many public health issues competing for resources in developing countries, and therefore, the optimal screening strategy will ultimately depend on the cost-effectiveness threshold of a given setting. For the poorest countries (those that can afford only $2 or $3 per year of life saved) a single lifetime screen using DVI, coupled with immediate treatment, may be the only feasible strategy. However, for countries that can afford up to $50 per year of life saved, a single lifetime screen using HPV may also be an attractive option. The cost-effectiveness of both of these screening strategies compares favorably with other public health interventions in low-resource settings such as childhood immunizations and AIDS prevention programs.

It is also important to recognize that our findings are based in part on data from several different studies, which varied in design and methodology. And while the most general findings are robust despite varying many of the parameters in ways that would reflect differences between geographic regions, the complete set of detailed results are not generalizable to countries other than South Africa. Country-specific differences for many of the inputs will need to be adjusted, though the model itself as a tool is applicable, given these adjustments.

Despite these qualifications, however, the findings clearly argue for accelerated efforts to test and apply novel screening methods for cervical cancer that are simple to establish, simple to perform, which have proven to be effective in field trials throughout the developing world, and which are affordable compared with existing investments in public health being made by developing nations.

The study was supported by funding from the Bill & Melinda Gates Foundation, through EngenderHealth, a member of the Alliance for Cervical Cancer Prevention.
Upcoming Professional Courses

In collaboration with the Center for Continuing Professional Education, the Harvard Center for Risk Analysis presents four important educational opportunities this Fall.

The Risk Communication Challenge, a three-day program, combines formal lectures with case-method teaching to help professionals in industry, medicine, government, and non-profit organizations learn how to strategically and effectively manage risk communication. The program treats risk communication as a complex challenge that requires a careful understanding of science, the mass media, stakeholder roles, ideologies, and lay conceptions of danger. Continuing education credits are available. A special European edition of the program will be offered in Brussels, Belgium Sept. 4-6, 2001. Ortwin Renn, PhD, will be the featured speaker. The program will be adapted for an American audience and presented Sept. 19-21, 2001 in Boston.

Course Directors Ragnar E. Lofstedt, George M. Gray, and David P. Ropeik.

Probabilistic Risk Analysis: Assessment, Management, and Communication, Sept. 4-7, at the Harvard School of Public Health. Course Directors Kimberly M. Thompson and David E. Burmaster designed this course for professionals who want to advance their knowledge of probabilistic risk analysis. Participants are expected to have a working knowledge of risk analysis and to feel reasonably confident about their abilities to apply mathematical reasoning and use computers for problem solving. Nationally and internationally known experts from different disciplines serve as faculty. Topics include characterizing variability and uncertainty in risk assessment, developing probabilistic models and model validation, implementing the analytic-deliberative process, and communicating uncertainty to the public.

Analyzing Risk: Science, Assessment, and Management, Oct. 2-5, at the Harvard School of Public Health. Course Director George M. Gray and expert faculty members help professionals develop key skills in risk assessment, management, and communication by examining complex problems involving chemicals and radiation and offering the opportunity to discuss important issues with leaders in the field.

For further information, or to register for any of these programs, consult: www.hsph.harvard.edu/ccpe or call the Center for Continuing Professional Education at 617-432-1171.

On July 19th, the United States Senate confirmed John D. Graham, founding director of HCRA, as Administrator of the Federal Office of Information and Regulatory Affairs in the Office of Management and Budget, Executive Office of the President.

An upcoming issue of Risk in Perspective will be devoted to the status of HCRA and energetic plans for strengthening our contribution to risk analysis and the decision sciences.