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Preventing Cervical and Anal Cancer in HIV-Positive Women and Men: Using Disease-Specific Models to Develop Clinical Guidelines

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In this issue of **RISK IN PERSPECTIVE**, we report the results of two studies conducted to evaluate the clinical benefits (life expectancy and quality-adjusted life expectancy), costs (U.S. dollars), and cost-effectiveness of screening for cervical and anal cancer in women and homosexual men infected with the human immunodeficiency virus (HIV).

WHAT CAUSES CERVICAL AND ANAL CANCER?

There is compelling evidence that a sexually transmitted virus called human papilloma virus (HPV) plays a critical etiologic role in the development of cervical and anal cancer. HPV is the most common sexually-transmitted virus, with about 74% of Americans having been infected with genital HPV at some point in their lives. Papilloma is a relatively small virus - basically two strings of DNA enclosed within a spherical protein shell. There are more than 70 types of this virus and they can infect nearly any cell on the skin or on the inner lining of tissues. Different types attack the skin of the hands and feet, others the lining of the mouth, and still others the genital tract. Each genital HPV type carries a unique risk of cancer and those associated with a high risk of cancer are referred to as "oncogenic" HPV types.

"Unlike many of the opportunistic infections associated with AIDS, the increased risk of cervical and anal cancer begins early in the course of HIV disease."

Cervical cancer is actually one of the best understood examples of how viral infection can lead to cancer. Cell division is regulated in large part by two proteins called Rb and p53. Two genes in the papilloma virus, E6 and E7, make proteins that attach themselves to p54 and Rb, respectively, and deactivate them, allowing cells to reproduce without constraint. The molecular changes caused by the papilloma virus result in cellular changes in the surface lining or "epithelium" of the genital tract. These changes result in "histopathologic abnormalities" that can be seen under a microscope and categorized as low-grade or high-grade squamous intraepithelial lesions (SIL). High-grade cervical SIL is believed to be the true precursor to cervical cancer. Because of the similarities in the biology, histopathology, and association with HPV, high-grade

anal SIL is likely to represent the precursor to anal cancer as well.

HOW DO WE SCREEN FOR CERVICAL AND ANAL CANCER?

The Pap smear was developed by Dr. George Papanicolaou in the 1930s and introduced for widespread cervical cancer screening in the 1940s. The Pap smear costs about $23 and requires a brief office exam, where cells are sampled from the cervix and affixed to a glass slide. The slide is examined under a microscope and abnormal cells are classified according to established universal criteria. If low-grade or high-grade SIL is identified the patient is referred for a more invasive test to make a conclusive diagnosis. Prevention of cervical cancer through Pap smear screening depends on the identification and treatment of high-grade SIL before it progresses to cancer. A single conventional Pap smear will detect 50-75% of cervical SIL or cancer. Widespread screening efforts in this country have resulted in a 40% decrease in the incidence and mortality associated with cervical cancer over the last two decades. In fact, cervical cancer screening in the general female population is one of the few interventions to receive an "A" recommendation from the U.S. Preventive Services Task Force.

Anal SIL in homosexual men has only recently been recognized as a clinical entity. The incidence of anal cancer in homosexual men, however, is increasing and currently approximates the incidence of cervical cancer prior to widespread screening 50 years ago. Recent studies have established that the Pap smear may also be used to detect anal SIL and its performance appears comparable to that in the cervix.

WHO IS AT HIGHEST RISK FOR PAPILLOMA VIRUS INFECTION AND CERVICAL AND ANAL CANCER?

Individuals who have impaired immune systems, such as those infected with HIV, are at higher risk for both genital HPV infection and HPV-induced SIL. The incidence of both cervical and anal cancer is also higher in HIV-positive women and HIV-positive homosexual men, respectively, compared with their HIV-negative counterparts. Unlike many of the opportunistic infections associated with end-stage AIDS, the increased risk of cervical and anal cancer begins early in the course of HIV disease.

In 1993 the U.S. Centers for Disease Control and Prevention (CDC) included cervical cancer among AIDS-defining conditions and recommended screening with two initial Pap smears, six months apart, followed by lifetime annual screening. These recommendations were debated with some advocating for more frequent screening, such as Pap smears every three to six months. Others argued that screening is expensive and time consuming, and because these women have a considerable risk of HIV-related mortality, they should not be screened at all. Motivated by this debate, we conducted a cost-effectiveness analysis of alternative screening strategies performed at different stages of HIV disease, in order to inform national clinical guidelines for HIV preventive health care.

Despite the growing body of evidence supporting an increased risk of anal cancer in HIV-positive homosexual men, it has yet to be considered an AIDS-defining diagnosis. Motivated by the absence of any recommendations for screening, we conducted an analysis to estimate the

clinical benefits and cost-effectiveness of potential screening strategies, explicitly incorporating the uncertainty in the natural history of high-grade al SIL.

THE DISEASE-SPECIFIC MODELS

Because prospective controlled clinical trials of cancer screening are often not feasible, policy makers have often relied on decision-analytic models to estimate the long-term consequences of a screening intervention. A Markov model is one type of decision-analytic model that is particularly useful for evaluating health interventions where there is an ongoing risk of disease (e.g. the progression of HIV disease to AIDS), when events can occur repeatedly (e.g. screening every year), and when events may occur at uncertain times (e.g. development of cancer). We developed such a model to depict the natural history of HPV-induced SIL and HIV disease, and simulated the process of screening, diagnosis, and treatment for cervical and anal cancer in hypothetical cohorts of HIV-positive women and homosexual men, respectively. The model captures important clinical characteristics which influence costs, prognosis, and health-related quality of life. Both the short and long-term clinical and cost consequences from screening, including the impact of false-positive and false-negative screening test results, are incorporated. We assumed that cervical SIL would be treated with laser therapy or loop electrosurgical excision, and that most high-grade cervical SIL would be treated with a minor surgical procedure. We assumed that low-grade anal SIL would not be treated but followed with surveillance screening every 6 months, and that high-grade SIL would be ted with surgical excision.

COST-EFFECTIVENESS ANALYSIS

We conducted a cost-effectiveness analysis to show the relationship between the resources used (costs) and the health benefits achieved (effects) for one screening strategy compared to an alternative screening strategy. The analysis was performed from the societal perspective and we followed the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. Morbidity and mortality consequences (net clinical risks and benefits) were expressed using a single measure, referred to as quality-adjusted life years (QALYs). Results are expressed using the cost-effectiveness ratio, defined as the additional cost of a specific screening strategy, divided by its additional clinical benefit, compared to the next least expensive strategy. We evaluated several screening strategies using cervical and anal Pap smears at different intervals.

Data for the natural history of HPV-induced SIL and HIV were obtained from prospective cohort studies and the published literature. Data for the effectiveness of new HIV treatments were obtained from randomized controlled trials. Costs of monthly HIV care were based on estimates from a large cost database. Health-related quality of life measures were obtained from several AIDS Clinical Trial Groups. Costs of cancer screening, diagnosis, and treatment protocols were estimated by applying Medicare average allowed charges to standard clinical treatment algorithms. For example, the cost of a Pap smear was $23, a diagnostic work-up $300, and treatment of a high-grade SIL about $4000, cancer from $10,000 to $40,000 depending on stage of disease.

COST-EFFECTIVENESS OF SCREENING TO PREVENT CERVICAL CANCER IN HIV-POSITIVE WOMEN

We found cervical cancer screening prolonged quality-adjusted life expectancy in HIV-positive women. Annual Pap smear screening after two smears six months apart was associated with a 2.6 month quality-adjusted life expectancy gain and cost $14,800 per QALY gained, compared with no screening. Screening less frequently prevented fewer cases of cancer, and despite lower screening costs was actually more expensive due to the high costs associated with the treatment of cervical cancer. Screening more frequently was more costly but provided only a few extra days of quality-adjusted life expectancy. The effectiveness of screening in women with late-stage HIV depended on the health-related quality of life in the years of life to be saved. For example, when quality-adjusted life expectancy fell below two years, the benefit of screening women in late stage HIV rapidly diminished.

COST-EFFECTIVENESS OF SCREENING TO PREVENT ANAL CANCER IN HIV-POSITIVE HOMOSEXUAL MALES

Anal cancer screening also increased quality-adjusted life expectancy at all stages of HIV disease, although similar to cervical cancer screening in women, the magnitude of the benefit was greatest in the earliest stages of HIV. Screening annually with anal Pap smears, beginning in early HIV disease, resulted in a quality-adjusted life expectancy gain of three months for $16,600 per QALY gained. Every six-month screening provided little additional benefit over that of annual screening and was much more expensive.

EVALUATING UNCERTAINTY

In a cost-effectiveness analysis, it is critical to examine the impact of the uncertainty in the data on the baseline results. These types of analyses are referred to as sensitivity analyses. For example, a "one-way sensitivity analysis" is when the analyst varies one uncertain parameter (e.g. the rate of progression of high-grade SIL to invasive cancer) over a plausible range and reports the effect on the estimates of clinical benefits, costs and cost-effectiveness. In both of our studies, the cost-effectiveness results were most influenced by the annual rate of high-grade SIL progression to cancer and the effectiveness of treatment for high-grade SIL. However, even taking into account a broad possible range of values for each of these parameters, annual screening in both men and women remained cost-effective. The availability of new drugs for HIV disease has resulted in dramatic decreases in HIV-related mortality. When we incorporated these data we found that clinical benefits of screening increased, most notably for persons with late-stage HIV disease, reflecting the longer life years at risk for SIL progression to invasive cancer.

COMPARISON OF HEALTH GAINS AND COST-EFFECTIVENESS RATIOS

The life expectancy gains associated with annual screening in both homosexual HIV-positive men and HIV-positive women are comparable or better than those associated with other preventive interventions in medicine. For example, Pap smear screening every three years in HIV-negative women provides 3.1 months, and 10 years of biennial mammography in women beginning at age 50, less than 1 month. It is also useful to compare our results with cost-effectiveness ratios for other accepted

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FURTHER READING

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preventive interventions in HIV disease. Prophylaxis for Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole costs $16,000 per QALY saved and prophylaxis for Mycobacterium avium complex costs from $35,000 to $74,000 per QALY saved (in 1995 U.S. dollars), both considered standard of care. Moreover, the quality-adjusted life expectancy gains associated with screening exceed nearly all gains associated with standard clinically recommended preventive interventions in HIV disease.

IMPACT OF THESE STUDIES

On the basis of these results our recommendation was that all HIV-positive women, regardless of stage of disease, be screened with two Pap smears six months apart followed by annual Pap smears, in agreement with the initial CDC recommendations. In view of the growing young HIV-positive female population in the U.S. and availability of with more effective but expensive treatments for HIV, use of inefficient screening strategies would represent an enormous opportunity cost. The 1999 U.S. Public Health Service HIV Clinical Guidelines Committee, therefore, did not change the national guidelines to include more frequent screening, electing instead to recommend annual cervical pap screening as the standard of care.

On the basis of these results screening HIV-positive homosexual men annually will also be cost-effective. However, it will be difficult to initiate a national screening program immediately because there is a shortage of trained clinicians to perform the diagnostic workup and treatment of anal SIL, and because anal Pap smear screening is not routinely performed and will require training. We recommended that immediate consideration be given to identifying such real world barriers associated with implementing a screening policy. Since our sensitivity analysis indicated that our results were most influenced by the progression rate of high-grade anal SIL to cancer, we also recommended these data be collected in future clinical studies.

These recommendations were presented at the 1999 U.S. Public Health Service HIV Clinical Guidelines Committee meeting and at the 1999 Centers for Disease Control sponsored national HPV research priorities meeting. As a result, the newest clinical guidelines acknowledge the higher risk of anal SIL and anal cancer in HIV-positive homosexual men for the first time since 1989, and clinical studies in these men have been assessed as high priority by relevant funding agencies. Finally, managed care organizations on the West Coast, where the HIV-positive homosexual population is considerable, have added screening as a covered preventive service.

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