How Often Should We Screen for Cervical Cancer?

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Over the past 60 years, the mortality from cervical cancer — once one of the most common and lethal cancers in women in the United States — has decreased dramatically. Much of the reduction has been due to the widespread use of the Papanicolaou test, which has enabled clinicians to detect cervical intraepithelial neoplasia before it progresses to cervical cancer and to detect cervical cancer at an early stage. When cervical cancer is detected early, the five-year survival rate is more than 90 percent.\(^1\) The Papanicolaou test is now the most widely used cancer-screening tool in the United States by far, with more than 80 percent of women undergoing screening in any two-year period and more than 90 percent having been screened at least once. By contrast, the rate of screening for colon cancer (by means of a fecal occult blood test) among women older than 50 years of age is only 34 percent within a two-year period.

Despite the widespread acceptance of cervical-cancer screening, questions remain about optimal screening strategies. One key question is the optimal frequency of testing. Cost–benefit analyses have suggested that lifelong annual screening may not result in substantially better outcomes than less frequent screening and is much more costly. With this in mind, the American Cancer Society recently revised its guidelines for screening,\(^2\) recommending intervals between screenings ranging from one to three years, depending on several factors, such as age, screening history, type of Papanicolaou smear, and history of immunosuppression. Other guidelines have also suggested screening less frequently than annually after three consecutive normal annual Papanicolaou tests and pelvic examinations. Yet there are not many data to support these recommendations.

In this issue of the Journal, Sawaya et al. (pages 1501–1509) report the rates of cervical neoplasia in a relatively high-risk cohort of women 30 to 64 years of age who had at least three previous negative Papanicolaou tests. They conclude that subsequent screening at three-year intervals would confer an excess risk of invasive cervical cancer of less than 3 in 100,000 — a risk that they note is roughly equal to the annual risk of breast cancer among men 45 to 64 years of age. This low risk might be lowered even further with improvements in the sensitivity of Papanicolaou testing achievable with liquid-based technology or human papillomavirus DNA testing and with adherence to new guidelines for the interpretation and appropriate follow-up of abnormal Papanicolaou tests.

Sawaya et al. also provide an estimate of the excess number of tests that would be required with continued annual screening. They estimate that in a hypothetical cohort of 100,000 women who have already had three normal consecutive Papanicolaou tests, annual screening, as compared with screening once three years after the last negative test, would result in an additional 69,665 Papanicolaou tests and 3861 additional colposcopic examinations in women 30 to 44 years of age and an additional 209,324 Papanicolaou tests and 11,502 colposcopic examinations in women 45 to 59 years of age, while detecting only one additional case of cancer. These additional tests are both costly and emotionally upsetting to the patient, without materially affecting the rate of cervical cancer.

Despite the guidelines indicating that the interval between screenings can be lengthened for many women, both physicians and patients have been reluctant to change it. This resistance probably stems from several factors, including the success and simplicity of annual screening, patients’ concern about cancer, and physicians’ concern about medicolegal issues. The data presented by Sawaya et al. may help to alleviate these worries.

A broader concern is that if the recommended interval between screenings were increased to three years, patients might inadvertently be tested even less frequently. Ensuring that women are tested no less frequently than every three years is important, since 10 percent of cases of cervical cancer occur in women who have had a Papanicolaou test but who have not been screened within the previous five years. As patients move away from annual cervical-cancer screening, we must make sure that they do
not discontinue screening entirely. Given the fact that half of all cases of cervical cancer occur in women who have never been screened, screening all women at least once would be expected to contribute more than continued annual testing to decreasing the mortality due to cervical cancer.

Given the evidence, what should practitioners do? For patients who are in categories with a low risk of cervical neoplasia and who are known to comply with screening recommendations, it is reasonable to lengthen the screening interval to three years after three negative Papanicolaou tests. For patients in higher-risk categories (such as those who have a history of cervical dysplasia or immunosuppression) or who do not comply with screening recommendations, it would be unwise to lengthen the screening interval. Regardless, a shift to a longer interval must be accompanied by systematic safeguards to ensure that women continue to undergo screening and that they are tested at safe intervals. Otherwise, we risk losing the impressive gains of the past 60 years.

Dr. Feldman reports having received an honorarium for serving as a consultant to Cytec.

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**Two Worlds of Malaria**

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Cases of malaria acquired by international travelers from industrialized countries probably number 25,000 annually; of these, about 10,000 are reported, and 150 are fatal. These numbers are growing because of increased international travel, an increased risk of transmission in areas where malaria control has faded, and the spread of drug-resistant strains of malaria. Yet these numbers remain very small in comparison with the global burden of malaria in the world’s malarious regions, where there are as many as 500 million cases annually and a death toll that takes the lives of 1 to 3 million children each year, mostly in Africa.

Chemoprophylaxis and other preventive measures continue to provide effective protection against malaria for the 30 million travelers who visit regions where malaria is endemic each year. Still, there is room for improvement in prophylactic regimens and in the diagnosis and treatment of travelers’ malaria when it occurs. In this issue of the Journal, Schwartz et al. (pages 1510–1516) report a new evaluation that reminds us of important issues in the recognition and management of the different forms of travelers’ malaria caused by the four species that infect humans: Plasmodium falciparum, P. vivax, P. ovale, and P. malariae.

After the demonstration at the end of the 19th century that malaria is transmitted by mosquitoes, a mystery remained about P. vivax malaria in northern Europe, where outbreaks occurred in the spring, before temperatures were warm enough for mosquitoes to transmit the parasites. The key to the puzzle came in 1948, when Shortt and Garnham found that parasites delivered by mosquitoes infect the liver before they begin the cycles of infection in red cells that cause disease (see Figure). It is now known that the liver stages of P. vivax and P. ovale can develop promptly or these species can remain latent as hypnozoite forms in the liver before emerging months to years later. These observations account for the epidemics in the early spring and also explain why a course of antimalarial drugs that are effective only against bloodstream parasites does not provide protection against subsequent relapses from the liver stages of P. vivax and P. ovale.

Most of the cases of malaria in the study by Schwartz et al. were detected within two months after the traveler’s return and can be attributed to inadequate prophylaxis. However, 1121 of the 3122 cases occurred 2 months to 4 1/2 years after the traveler’s return. These late presentations consisted almost entirely of P. vivax and P. ovale malaria caused by hypnozoites that were unaffected by prophylaxis with blood-stage antimalarial drugs. The cases of P. falciparum and P. malariae malaria in patients with late presentations were most likely caused by blood-stage parasites that were drug-resistant or had survived incomplete prophylaxis.