# HPV testing for cervical cancer may be safe at longer intervals than what current guidelines recommend

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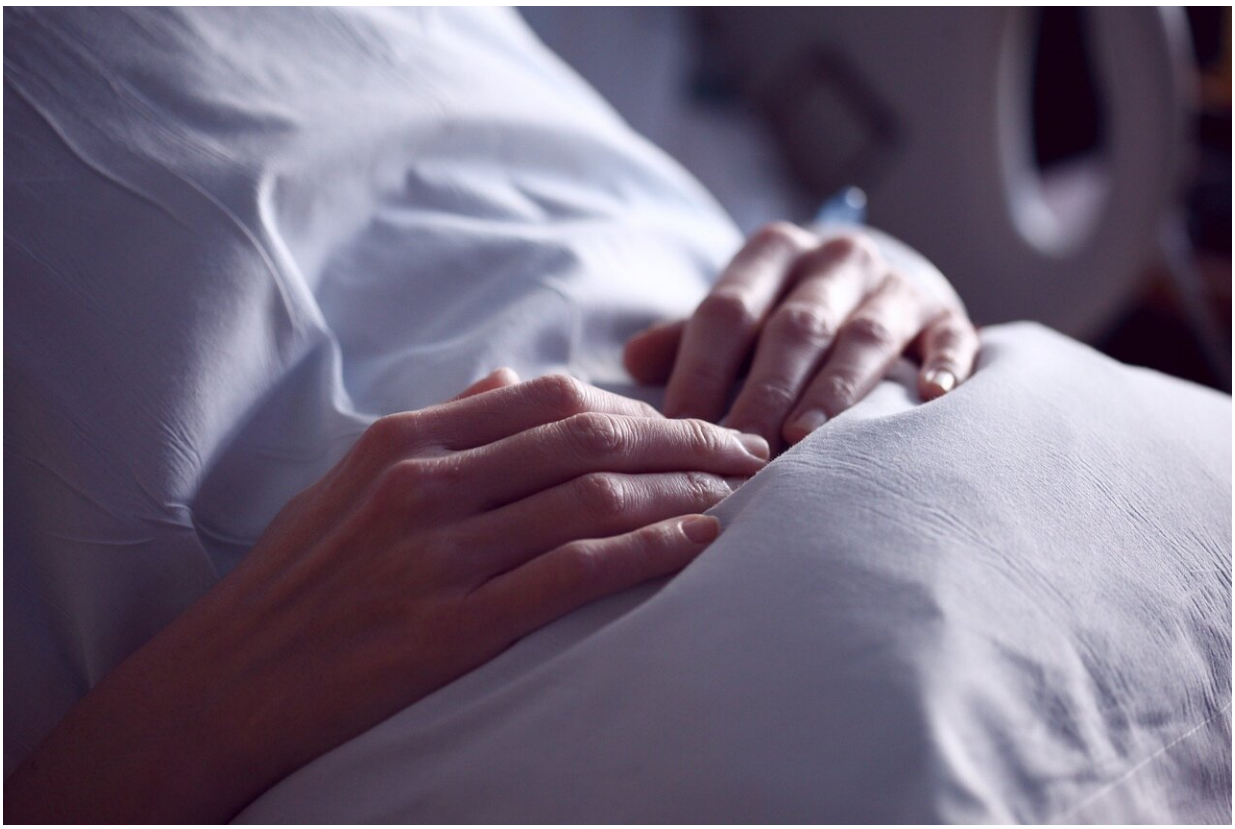

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Over the past two decades, the United States has been transitioning from cytology to HPV-based screening for cervical cancer. The U.S.

Preventive Services Task Force currently recommends one of three options for routine cervical cancer screening: 1) cytology screening every three years; 2) HPV screening every five years; or 3) co-testing in which both an HPV and cytology screening are conducted every five years.

"There is currently a global shift from conventional cervical cancer screening methods like cytology, or the Pap smear, to HPV-based screening because HPV-based screening has a higher sensitivity to detect precancerous lesions," Gottschlich said.

"However, some have expressed concern that the longer interval between HPV screens may increase the risk for the development of cervical cancer. These findings should provide assurance that the five-year interval recommended for HPV screening is even safer than the three-year interval for cytology screening."

Due to available high-performance screening methods, such as the HPV test, and the HPV vaccine, cervical cancer is highly preventable, which is why the World Health Organization (WHO) has called for the global elimination of cervical cancer by 2030; defined as reducing new cases to four or fewer per 100,000 annually.

Even though many high-income countries have established cytology-based screening programs, which have led to decreased incidence rates, many still have rates above the WHO's elimination threshold goal, including in the United States where incidence is 7.6 per 100,000 individuals, according to federal statistics.

As more countries adopt HPV screening programs to accelerate the elimination of cervical cancer, Gottschlich said questions remain about the optimal interval between screens, which is why she and her colleagues designed a study to investigate the long-term risk of cervical

precancer after negative HPV screening compared to after negative cytology screening, the latter of which has been used to guide previous screening recommendations.

In this longitudinal study, published in *Cancer Epidemiology, Biomarkers & Prevention*, they examined data from four cohorts of women and individuals with a cervix:

1. 5,546 who had one negative HPV screen;
2. 6,624 who had two consecutive negative HPV screens four years apart;
3. 782,297 who had one negative cytology screen; and
4. 673,778 who had two consecutive negative cytology screens two to three years apart.

Gottschlich and colleagues used data from the Canadian HPV For Cervical Cancer Prevention (HPV FOCAL) randomized trial conducted between January 2008 through December 2016 and its 14-year longitudinal follow-up FOCAL-DECADE study for the HPV screening cohorts.

Data were used from the British Columbia Cervix Screening Program during the same interval for the cytology cohorts. Participants from each cohort were between the ages of 25 and 65 at the initial screen.

Cumulative risk of cervical intraepithelial neoplasia grades 2 (CIN2), 3 (CIN3), and higher (referred to as CIN2+ or CIN3+)—which are premalignant lesions of cervical cancer—were calculated for each cohort. The risk of CIN2+ eight years after one (3.2/1,000) or two (2.7/1,000) negative HPV test(s) was similar to that of three years after one (3.3/1,000) or two (2.5/1,000) negative cytology screen(s).

After six years, longer than current five-year guidelines, HPV screens

showed lower risk after both one (2.5/1,000) and two (2.3/1,000) negative tests. Risk of CIN3+ was also lower or similar in the HPV cohorts following eight years compared to the cytology cohorts after three years.

While risk for CIN2+ was higher for HPV screening for intervals longer than eight years compared to cytology after three years, the detection of cervical precancer still remained low after negative HPV screening during the 14-year duration of the study period and was significantly lower than normal cytology screening over that period.

"HPV screening performs better than cytology by detecting more precancer earlier, which can then be treated earlier," Gottschlich said. "We saw that in our study population, even those who had only one negative HPV test were at very low risk for the development of cervical precancer for many years after the negative test."

Gottschlich said that these results could better inform updated screening guidelines for cervical cancer, but each country or province will need to determine the right guidelines given their populations and the resources at their disposal.

"Policy leaders need to consider a broad array of factors in health decision-making in their settings when considering how to prioritize HPV-based screening over cytology," Gottschlich said. "Optimal implementation strategies depend on the kind of screening engagement and resources available in each specific program."

Gottschlich noted that it is also important to consider the potential loss to follow-up that comes with long screening intervals. "Extending intervals require health system considerations to ensure adequate continued engagement to minimize loss to follow up," she said.

Longer intervals between testing, however, could allow for the realignment of resources to reach under-screened or unscreened populations and to encourage follow-up, Gottschlich added. "Screening alone is not sufficient to eliminate cervical cancer. We need to ensure that women who have an abnormal screen have access to diagnostic follow-up and treatment if necessary."

Future studies will continue to follow these cohorts to better understand optimal implementation strategies for HPV screening, including appropriate ages for entry and exit into screening and triage management strategies.

Limitations of this study include the fact that even though participants in the HPV FOCAL were randomly assigned at the start of the trial, differences in drop-out and screening rates may have made the HPV groups less comparable over the course of the study; however, loss to follow-up was low. Additionally, co-testing was used during exit screens, where two cases of CIN2+ were caught in cytology that were missed by the HPV test.

Gottschlich said this did not affect the main findings as a previous study found that cytology missed over eight times more CIN2+ compared to HPV screening. Also, the study was conducted in a population that was very well screened, so the results are not directly applicable to low-resource settings.

**More information:** Anna Gottschlich et al, Evidence of decreased long-term risk of cervical pre-cancer after negative primary HPV screens compared to negative cytology screens in a longitudinal cohort study, *Cancer Epidemiology, Biomarkers & Prevention* (2024). DOI: 10.1158/1055-9965.EPI-23-1587