Is vaginal estrogen used for GSM associated with a higher risk of CVD or cancer?

**No.** Vaginal estrogen use (average duration of use, 37.5 months) for genitourinary symptoms of menopause (GSM) was not associated with a higher risk of cardiovascular disease (CVD) or cancer in nonusers of systemic hormone therapy in the Nurses’ Health Study. During 18 years of follow-up for the almost 900 postmenopausal users of vaginal estrogen, compared with about 53,000 nonusers, the risks of CVD, cancers, and hip fractures were not different between groups. Presence or absence of a uterus did not change the study results.

**EXPERT COMMENTARY**

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GSM, a chronic and often progressive condition, occurs in almost 50% of postmenopausal women and has been shown to impair sexual function and quality of life. Symptoms include vaginal dryness, vulvar or vaginal itching, dyspareunia, urinary urgency or frequency, and increased urinary tract infections. Although lubricants or vaginal moisturizers may be sufficient to treat GSM, targeted hormonal therapy may be needed to improve the symptoms and resolve the underlying cause, due to vaginal hormone loss.

Despite lack of any observational or clinical trial evidence for chronic health disease risks related to low-dose vaginal estrogen use, there remains an US Food and Drug Administration boxed warning on the package label for low-dose vaginal estrogen related to risks of heart disease, stroke, venous thromboembolism, pdementia, and breast cancer. The objective of the investigation by Bhupathiraju and colleagues was to evaluate associations between vaginal estrogen use and health outcomes, including CVD (myocardial infarction, stroke, and pulmonary embolism/deep vein thrombosis), cancer (total invasive, breast, endometrial, ovarian, and colorectal), and hip fracture.

**Details of the study**

The prospective analysis included 896 postmenopausal current users of vaginal estrogen in the Nurses’ Health Study (NHS; 1982–2012), compared with 52,901 nonusers. Eighteen years of follow-up was evaluated. Users of systemic hormone therapy were excluded from the analysis. For the NHS, self-reported data were collected every 2 years on questionnaires for vaginal estrogen use and...
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health outcomes. Investigators used medical records to confirm health outcomes.

After adjusting for covariates, no significant differences in risks were found for CVD, cancer, and hip fracture between users and nonusers of vaginal estrogen, regardless of hysterectomy status.

**Key findings**

After adjusting for multiple variables (including age, race, physical activity, age at menopause, hysterectomy, aspirin use, parental history of cancer, etc), health outcomes for CVDs, all cancers, and hip fracture were:

- myocardial infarction: hazard ratio (HR), 0.73 (95% confidence interval [CI], 0.47–1.13)
- stroke: HR, 0.85 (95% CI, 0.56–1.29)
- pulmonary embolism/deep vein thrombosis: HR, 1.06 (95% CI, 0.58–1.93)
- hip fracture: HR, 0.91 (95% CI, 0.60–1.38)
- all cancers: HR, 1.05 (95% CI, 0.89–1.25).

Health outcomes for specific invasive cancers (risk for endometrial cancer included only women with an intact uterus) were:

- invasive breast cancer: HR, 1.07 (95% CI, 0.78–1.47)
- ovarian cancer: HR, 1.17 (95% CI, 0.52–2.65)
- endometrial cancer: HR, 1.62 (95% CI, 0.88–2.97)
- colorectal cancer: HR, 0.77 (95% CI, 0.45–1.34).

**Study strengths and weaknesses**

A causal relationship cannot be proven as the study was observational. However, a strength included the 18 years of follow-up. Women used vaginal estrogen for an average of 3 years, which provided longer-term safety data than available 12-month clinical trial data. Data were collected through self-report on questionnaires every 2 years, which is a drawback; however, participants were registered nurses, who have been shown to provide reliable health-related information. Comparisons between therapies were not possible as data were not collected about type or dosage of vaginal estrogen. Available therapies during the NHS included vaginal estrogen tablets, creams, and an estradiol ring, with higher doses available during earlier parts of the study than the lower doses commonly prescribed in current day.

**Overall**

The findings from this long-term follow-up of the NHS provide support for the safety of vaginal estrogen for treatment of GSM. No statistically significant increased health risks were found for users of vaginal estrogen, similar to earlier reported findings from the large Women’s Health Initiative.² Low-dose vaginal estrogen is recommended for treatment of GSM by The North American Menopause Society, the American College of Obstetricians and Gynecologists, and the Endocrine Society.

Absorption of low-dose vaginal estrogen preparations appears minimal, and they are effective and generally safe for the treatment of GSM for women at any age. Progesterone is not recommended with low-dose vaginal estrogen therapies, based primarily on randomized clinical trial safety data of 12 months.³ Postmenopausal bleeding, however, needs to be thoroughly evaluated. For women with breast cancer, include the oncologist in decision making about the use of low-dose vaginal estrogen. ●

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

Despite the boxed warning on vaginal estrogen, the findings from this study support the safety of vaginal estrogen use for effective relief of GSM in women with and without a uterus. JOANN V. PINKERTON, MD, NCMP

**References**


**FAST TRACK**

Low-dose vaginal estrogen is effective and generally safe for treating GSM in women of any age