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VAGINALE ESTROGENS AFTER BREASTCANCER: EVIDENZE-BASED CLAASIFICATION OF RISKS

Schweizerische Gesellschaft für Gynäkologische Endokrinologie, Kontrazeption und Menopause

NEWSLETTER JUNE 2025

Beste ME, Kaunitz AM, McKinney JA, Sanchez-Ramos L.

Vaginal estrogen use in breast cancer survivors: a systematic review and meta-analysis of recurrence and mortality risks.

Am J Obstet Gynecol. 2025 Mar;232(3):262-270.e1.

BACKGROUND

Menopausal genitourinary syndrome (GSM) is a common consequence of oncological treatment in women with breast cancer. It includes vaginal atrophy, dyspareunia, recurrent urinary tract infections and a significant reduction in quality of life. Aromatase inhibitors in particular exacerbate GSM symptoms due to consistent oestrogen deprivation.

Although vaginal estrogens are considered the most effective treatment option, there are considerable concerns regarding their use in women with a history of breast cancer - particularly due to regulatory requirements (e.g. EMA contraindication) and a lack of randomized studies. In practice, this often leads to therapeutic restraint, even in highly symptomatic patients.

STUDY

The current systematic review and meta-analysis examined the safety of vaginal estrogens with regard to breast cancer recurrence and breast cancer-specific and all-cause mortality. Eight high-quality observational studies (n = 61,695) were included in which only vaginal, non-systemic estrogen preparations were used.

In most studies, preparations containing estradiol (tablets, creams, vaginal rings) were used. Some studies also included products containing estriol (e.g. low-dose creams or vaginal suppositories). The exact formulation was not specified in all studies; when specified, estradiol preparations predominated.

The documented duration of treatment in most studies was between 1 year and over 10 years (Agrawal et al.: mean duration 1 year; Dew et al.: average 5.5 years; O'Meara et al.: up to 10 years; in other studies, the duration of treatment was not specified exactly, but was described as "long-term"; the Sund study explicitly differentiated between short-term (<90 days) and long-term use (>90 days).

RESULTS OF THE META-ANALYSIS

- Breast cancer recurrence: No increased risk (OR 0.48; 95% CI 0.23-0.98), but high heterogeneity ($I^2 = 95.8\%$), fragility index = 1.
- Breast cancer-specific mortality: No significant increase (OR 0.60; 95% CI 0.18-1.95), robust result (reverse FI = 69).
- All-cause mortality: Significantly reduced (OR 0.46; 95% CI 0.42-0.49), without heterogeneity ($I^2 = 0\%$).

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COMMENT

This meta-analysis is the first to provide comprehensive and systematically reviewed evidence on the safety of vaginal oestrogens in women with breast cancer. The results speak against an increased risk from the use of local estradiol or estriol preparations - even when used for several years. The continuing "healthy user bias" - i.e. the tendency to prescribe to healthier, more sexually active patients with a better prognosis - could partly explain the observed reduction in mortality. Nevertheless, the consistently low systemic estrogen levels under vaginal therapy and the lack of risk increase in subgroup analyses support the assumption of safe use. The meta-analysis strengthens the position of vaginal estrogens as a safe and effective treatment option for GSM after breast cancer. As gynecologists, we are called upon to provide evidence-based and individualized advice - instead of rejecting it across the board.

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