# HORMONE REPLACEMENT THERAPY AND BREAST CANCER RISK

TITLE: The use of estrogens and progestins and the risk of breast cancer in postmenopausal women
AUTHORS: Colditz GA, Hankinson SE, Hunter DJ, et al
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***Clinical question.*** **Does hormone replacement therapy increase the risk of breast cancer in postmenopausal women?**

*Background.* Postmenopausal hormone replacement therapy (HRT) is known to have a number of effects, both positive and negative, on women's health. The question of whether the hormone replacement therapy most commonly used in the United States, conjugated estrogens in combination with progestin, increases the risk of breast cancer has been controversial.

*Population studied.* The study initially enrolled 69,586 women in the Nurses' Health Study who were postmenopausal by 1990 or earlier. Women were excluded if they had breast or other cancer at the time of enrollment in the study (1976). Follow-up of the cohort for nonfatal breast cancer was 95% complete, and for fatal breast cancer was more than 98% complete.

*Study design and validity.* A large cohort study (one in which a large group is followed over time) with information gathered at regular intervals and excellent rates of long-term follow-up provides the strongest type of evidence for assessment of causal relationships short of a randomized trial. In this study, follow-up was conducted at 2-year intervals, and responses to questionnaires were used to define HRT use. The researchers controlled for other known risk factors for breast cancer by stratified and proportional hazards analyses. Data were followed until the date of diagnosis of breast cancer, or the date of death, or June 1, 1993.

For each woman dying from breast cancer, 10 women were selected at random from the cohort of women who were free from breast cancer, matched by year of birth and age at menopause. This is known as a "nested case-control design," because a case-control study is nested within the larger cohort study. Logistic regression analysis was used to calculate the adjusted odds ratio (an estimate of relative risk) for death from breast cancer.

*Outcomes measured.* The main outcome measures were diagnosis of invasive breast cancer and death from breast cancer. Outcomes were initially identified based on responses to questionnaires sent at 2-year intervals. The National Death Index was searched for deaths among nonresponders; pathology reports were obtained for 93% of these cases. Cases of carcinoma in situ were excluded (n=157).

*Results.* A total of 1935 cases of breast cancer in postmenopausal women were identified during 725,550 person-years of follow-up. A person-year is one person followed for 1 year. The relative risk of breast cancer for HRT users, after adjusting for risk factors, was 1.32 (95% confidence interval [CI], 1.14 to 1.54) for conjugated estrogens alone, 1.41 (95% CI, 1.15 to 1.74) for combined HRT, and 2.24 (95% CI, 1.26 to 3.98) for progestins alone. The adjusted relative risk increased with increasing duration of current HRT use, ranging from 1.14 for 1 to 23 months of use, to 1.46 for 120 months or more of use. The adjusted relative risk of breast cancer for past hormone use was not increased. There were 359 deaths attributed to breast cancer among women who were postmenopausal at the time of diagnosis. The adjusted odds ratio for death from breast cancer was 1.14 (95% CI, 0.85 to 1.51) among women who were HRT users at the time of diagnosis. For women with 5 or more years of use, the odds ratio was 1.45 (95% CI, 1.01 to 2.09).

***Recommendations for clinical practice.*** **This large, well-designed study represents the strongest evidence to date that HRT, including combined HRT, leads to an increased risk of breast cancer with 5 or more years of use. While the magnitude of the increased risk is not large, breast cancer is a common disease. A recently published case-control study did not show this association, but the design in that study is weaker and the number of cases substantially smaller *(Stanford JL, Weiss NS, Voigt LF, et al. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 1995; 274: 137–42).* When counseling perimenopausal patients about the benefits and risks of HRT, the small increased risk in breast cancer should be weighed against the benefits gained from decreased risk of heart disease and osteoporosis, and the control of**

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**menopausal symptoms. Other than control of symptoms, more than 5 years of therapy is required for manifestation of either risks or benefits. As the risk profile will differ for each patient considering HRT, family physicians must individualize their recommendations. Decisions will be best made jointly between physician and patient, in the context of a frank discussion of all the potential benefits and risks.**

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## CLINICAL ASSESSMENT OF DEEP-VEIN THROMBOSIS

TITLE: Accuracy of clinical assessment of deep-vein thrombosis
AUTHORS: Wells PS, Hirsh J, Anderson DR, Lensing AWA, et al
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***Clinical question.*** **Is the clinical examination useful for estimating the probability of deep-vein thrombosis (DVT) in nonhospitalized patients?**

*Background.* It is not uncommon for an office-based physician to assess a patient with pain or swelling in a lower extremity. Estimating the chance that DVT is present should be central to the decision of whether to send the patient for further evaluation. Once test results are known, this same estimate could help the physician calculate the posttest probability of DVT.

Earlier studies have suggested that the clinical examination and history are not very helpful in diagnosing DVT; however, these studies focused on hospitalized patients.[1,2] The diagnostic value of signs and symptoms can be very different in the outpatient setting.[3] Previous studies also overlooked some data readily available to physicians, including a patient's risk factors for DVT and whether there was another likely diagnosis for a patient's findings. This study addresses these deficiencies.

*Population studied.* All outpatients referred for the evaluation of suspected DVT were invited to enter the study if they did not have a history of prior DVT or pulmonary embolus (PE), were not pregnant, did not have a lower extremity amputation, were not suspected to currently have a PE, and if the duration was less than 60 days. What this study does not include are the patients who were not referred to the hospital because the office-based physicians who assessed them did not feel hospital evaluation was warranted.

Table. Factors Predictive of Deep Vein Thrombosis

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|---|
| Major factors |
| Active cancer |
| Paralysis or recent casting of a lower extremity |
| Recently bedridden for more than 3 days and/or major surgery within 4 weeks |
| Localized tenderness along the deep venous system |
| Swollen thigh and calf (by measurement) |
| Calf swelling >3 cm on symptomatic leg |
| Strong family history of DVT |
| Minor factors |
| Hospitalization in previous 6 months |
| Trauma to leg in past 60 days |
| *In the symptomatic leg only:* |
| Pitting edema |
| Dilated superficial veins (nonvaricose) |
| Erythema |

High probability (85% will have DVT): *No alternative diagnosis with a minimum of either 3 major factors or 2 major and 2 minor factors.*
Low probability (5% will have DVT): *(1) No alternative diagnosis with a maximum of either 1 major factor and 1 minor factor, or no major factors and 2 minor factors; (2) an alternative diagnosis with a maximum of either 1 major factor and 2 minor factors, or no major factors and 3 minor factors.*
Moderate probability (33% will have DVT): *All patients without a high or low probability of DVT.*

*Study design.* The study was a prospective investigation in the outpatient departments of three medical centers, two in Canada and one in Italy. Clinical data included results of the physical examination, any recent history of immobilization, surgery, cancer, or trauma, and any strong family history of DVT. At two centers, patients also underwent compression ultrasonography, interpreted by a panel who were blinded to the clinical history and other test data.

Contrast venography, which all patients underwent, was the "gold standard" with which clinical estimation was compared. Contrast venography was interpreted by a panel blinded to the patient's clinical history and the results of any other imaging tests. The result of the index test (clinical estimation) was not used to decide whether the gold standard test was performed. When patients came to the hospital, they were entered into the study before any clinical data were collected.

*Results.* The investigators created a checklist of seven major and five minor factors, which, when combined with knowledge about alternative diagnoses, accurately predicted the probability of DVT (Table).

There was excellent agreement between physicians when they independently collected the clinical data. The percentage of patients in each diagnostic category that actually had DVT did not differ significantly at the three study sites. Compression ultrasonography was found to have high specificity in all three probability groups (98% to