

# Postmenopausal Estrogen Therapy and the Risk for Developing Systemic Lupus Erythematosus

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**Objective:** To examine the relation between postmenopausal hormone use and development of systemic lupus erythematosus.

**Design:** Prospective cohort study.

**Setting:** Nurses' Health Study.

**Patients:** 69 435 women aged 30 to 55 years in 1976 who reported that they had completed menopause and did not have systemic lupus erythematosus or any connective tissue disease were followed every 2 years from 1976 to 1990. These women were classified as never-or ever- (current and past) users of postmenopausal hormones.

**Measurements:** Incidence rates of systemic lupus erythematosus and classification criteria from the American College of Rheumatology that were confirmed by chart review.

**Results:** With never-users of postmenopausal hormones as the reference group, age-adjusted relative risks for systemic lupus erythematosus (n = 45 women) were 2.1 (95% CI, 1.1 to 4.0) for ever-users, 2.5 (CI, 1.2 to 5.0) for current users, and 1.8 (CI, 0.8 to 4.1) for past users. A proportional increase in the risk for systemic lupus erythematosus was observed that was related to the duration of use of postmenopausal hormones (test for trend, P = 0.011).

**Conclusions:** Postmenopausal hormone therapy is associated with an increased risk for developing systemic lupus erythematosus.

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Systemic lupus erythematosus is an autoimmune disease of unknown cause. Risk factors proposed as important in the pathogenesis of systemic lupus erythematosus include genetic, environmental, and hormonal factors [1]; strong evidence implicates sex steroid hormones in the pathogenesis of this disease [2]. Whether postmenopausal hormone therapy is associated with an increased risk for developing systemic lupus erythematosus has not been previously studied.

To examine the relation between postmenopausal hormone use and the development of systemic lupus erythematosus, we analyzed data from the Nurses' Health Study cohort. On the basis of 14 years of follow-up, we evaluated the effect of never-use, ever-use, current use, and duration of postmenopausal hormone use on the incidence of systemic lupus erythematosus.

## Methods

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## The Nurses' Health Study Cohort

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In June 1976, the Nurses' Health Study cohort was assembled using questionnaires mailed to all female, married registered nurses aged 30 to 55 years living in 11 states. The questionnaires sought information on various diagnoses, exposures, and health practices. Biennial questionnaires have subsequently been completed to update the information and to document the occurrence of major health conditions.

### Ascertainment of Postmenopausal Hormone Use

In 1976, women in the cohort were asked whether they had taken hormone supplements after menopause and, if they had, for how long. Information on hormone use, including the type of hormone taken, was updated in subsequent questionnaires sent every 2 years until 1990, with explicit questions about current use and duration of use in the intervening 2 years. We calculated time since last use for past users. Because body mass index and cigarette smoking may modify levels of endogenous estrogens, adjustment for these variables was included in the analysis.

### Case Definition of Systemic Lupus Erythematosus

Questions about the diagnosis of any rheumatic condition since 1976 were included on every questionnaire from 1980 onward. Systemic lupus erythematosus was included in the 1982, 1984, 1986, and 1992 questionnaires. In addition, questions about "other major illnesses diagnosed" were included in every biennial questionnaire. We mailed a validated screening questionnaire [\[3\]](#) to all participants who reported any rheumatic, musculoskeletal, or connective tissue disease. Overall, 87% of nurses responded to this questionnaire, which has a sensitivity of 96% and a specificity of 86% for systemic lupus erythematosus [\[3\]](#).

Medical records were obtained for all potential cases of a systemic rheumatic disease identified by questionnaire. The medical record for each case was reviewed independently by two rheumatologists blinded to exposure information, and a case was defined using classification criteria for systemic lupus erythematosus from the American College of Rheumatology (ACR) [\[4\]](#). "Definite" cases required at least four criteria. The use of strict criteria for diagnosing systemic lupus erythematosus biases against the inclusion of milder or atypical cases or patients who do not fulfill criteria early in their disease; thus, using such criteria could underestimate the true incidence of the disease. We therefore separately analyzed two additional groups of patients that were not mutually exclusive and that probably had systemic lupus erythematosus: 1) patients meeting three or more ACR criteria for systemic lupus erythematosus and 2) patients diagnosed by their physicians as having systemic lupus erythematosus, even if they did not meet enough classification criteria by chart review. When the rheumatologists disagreed about whether a specific criterion was present, the complete medical information was reviewed by a third independent rheumatologist and a final judgment was made.

### Participants

Postmenopausal women for whom information on hormone use was missing were excluded from the analysis. Postmenopausal status has previously been defined. Information from the women in this cohort about whether they had reached menopause was highly accurate [\[5\]](#).

In 1976, 23 582 postmenopausal women entered the analysis for the period from 1976 to 1978. This group was expanded to include women who subsequently reached menopause. During the 14 years from 1976 to 1 June 1990, we accrued 631 551 person-years of follow-up among 69 435

postmenopausal women. Only women with systemic lupus erythematosus whose condition was diagnosed between June 1976 and 31 May 1990 were included. To identify women free from systemic lupus erythematosus at each baseline period, those in whom the disease was diagnosed at the beginning of each time period were excluded from subsequent follow-up.

## Statistical Analysis

For each participant, the person-time was allocated to categories of hormone use, first according to the information gathered in 1976 and thereafter according to the updated information obtained in the subsequent questionnaires. Person-time was calculated from 1976 until 31 May 1990, the date of diagnosis of systemic lupus erythematosus, the time patients were lost to follow-up, or death, whichever came first. The person-time of follow-up was reassigned according to the respondent's current status at the beginning of each of the 2-year intervals. If no questionnaire was returned for a 2-year follow-up period and a woman's previous status had been "current hormone use," the woman was classified in the update as "missing for hormone use" for that 2-year interval. Incident cases of systemic lupus erythematosus were allocated to the exposure status reported at the beginning of the interval during which the diagnosis had been made.

The analysis is based on incidence-density rates using person-years of follow-up as the denominator and relative risk (RR) as the measure of association. We computed age-adjusted RRs with 95% CIs [6]. The Mantel extension test [6] for trend was used to assess dose-response relations; all P values are two-tailed.

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## Results

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During 631 551 person-years of follow-up, 45 "definite" cases of systemic lupus erythematosus were confirmed. Women currently using postmenopausal hormones accounted for 21.7% of the total follow-up time; past hormone users accounted for 26.1%; and women who had never used hormones accounted for 52.2%. The number of cases and the incidence rates per 100 000 women were as follows: 15 cases in women who had never used hormones (incidence, 4.5) and 30 cases in women who had ever used hormones (incidence, 9.9). Among women who had ever used hormones, 18 cases occurred among current users (incidence, 13.1) and 12 among past users (incidence, 7.3). Compared with never-users, ever-users of postmenopausal hormones had an age-adjusted RR of 2.1 (95% CI, 1.1 to 4.0). Among ever-users, current users had an age-adjusted RR of 2.5 (CI, 1.2 to 5.0) and past users had an age-adjusted RR of 1.8 (CI, 0.8 to 4.1) [Table 1](#).

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### Table 1. Use of Postmenopausal Hormones and Age-Adjusted Relative Risk for Systemic Lupus Erythematosus

We examined whether any association existed between duration of use or the time since the last use of postmenopausal hormones and the risk for systemic lupus erythematosus [Table 2](#). Overall, a proportional increase in the risk for developing systemic lupus erythematosus was seen according to the duration of use of postmenopausal hormones: Women who used postmenopausal hormones for 1 to 4 years had an age-adjusted RR of 1.8 (CI, 0.9 to 3.8), those who used hormones for 5 to 10 years had an age-adjusted RR of 2.7 (CI, 1.2 to 6.4), and those who used hormones for more than 11 years had an age-adjusted RR of 3.5 (CI, 1.2 to 10.9) (test for trend,  $P = 0.01$ ). Although we also observed that the increased risk for developing systemic lupus erythematosus decreased with time after the last use of postmenopausal hormones, this trend was not significant ( $P = 0.44$ ).

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### Table 2. Characteristics of Postmenopausal Hormone Use and Age-Adjusted Relative Risk for Systemic Lupus Erythematosus

Among the two groups of patients defined as probably having systemic lupus erythematosus, 72 patients met three or more ARC criteria: In this group, ever-users of postmenopausal hormones had an age-adjusted RR of 1.6 (CI, 1.0 to 2.6) compared with never-users. Among ever-users, current users had an age-adjusted RR of 2.2 (CI, 1.3 to 3.7) and past users had an RR of 1.1 (CI, 0.6 to 2.1) [Table 1](#). A physician diagnosis of systemic lupus erythematosus was confirmed by medical records from 65 patients; this was independent of meeting enough classification criteria by chart review to fulfill ACR criteria for systemic lupus erythematosus. In this group, ever-users of postmenopausal hormones had an age-adjusted RR of 1.7 (CI, 1.1 to 2.9) compared with never-users. Among ever-users, current users had an age-adjusted RR of 2.1 (CI, 1.2 to 3.7), and past users had an RR of 1.4 (CI, 0.7 to 2.7) [Table 1](#). For definite cases, we observed an association between the duration of use or the time since the last use of postmenopausal hormone therapy and the risk for the disease in both groups of patients who probably had systemic lupus erythematosus (data not shown).

Among 45 patients meeting four or more criteria for systemic lupus erythematosus, 40 had a diagnosis of systemic lupus erythematosus confirmed by a physician (27 (60%) confirmed by an ACR-certified rheumatologist). When we restricted the analysis to these 40 patients, the results did not change [Table 1](#). The age-adjusted RR for systemic lupus erythematosus among postmenopausal hormone users after adjustment for smoking was similar to that seen after adjustment for age only (data not shown). Further adjustment for body mass index did not change the magnitude or direction of the association (data not shown).

## Discussion

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In this large prospective cohort study of 69 435 women with 631 551 person-years of follow-up, use of postmenopausal hormone therapy was associated with an increased risk for systemic lupus erythematosus compared with no use of postmenopausal hormones. Among ever-users, the risk for systemic lupus erythematosus was higher in current users than in past users. This association was directly proportional to the duration of use and inversely proportional to the time since the last use of postmenopausal hormone therapy, although the trend was not statistically significant.

Several potential limitations of this study must be considered. Because information on exposure to estrogen was based on self-reports, postmenopausal hormone use may have been misclassified; however, misclassification should be minimal because the study participants were registered nurses with a proven interest in medical research. Self-report in general has been highly accurate in this cohort [7]. Further, any random misclassification in hormone use would lead to an underestimate of the true association. The prospective design of this study precludes the possibility that these results are explained by recall bias.

Another potential source of bias is the possibility that increased opportunity for diagnosis of systemic lupus erythematosus might have occurred among women using hormones because they had to be under active medical care. However, 87% of participants reported at least one visit to a physician or clinic between 1988 and 1990; thus, biased ascertainment of cases is unlikely. In addition, confounding by indication for estrogen use (whereby women at high risk for systemic lupus erythematosus are selectively prescribed postmenopausal hormones) is unlikely.

Of major concern is the complexity of diagnosing systemic lupus erythematosus. Cases of systemic lupus erythematosus were identified through a multistep procedure of self-reported diagnosis, supplementary questionnaire, and medical information. Application of strict criteria for diagnosing systemic lupus erythematosus may underestimate the true incidence of disease. With a rare disease, a slight underestimate of incidence rates is less important in a study of causation than is misclassification of participants without disease as having disease [7]. Although no other study has addressed the relation of postmenopausal hormone therapy to the risk for developing systemic lupus erythematosus, the congruity of several observations contributes to the biological plausibility of an adverse role of postmenopausal estrogen therapy in the development of systemic lupus erythematosus. Female sex is considered the strongest risk factor for the development of systemic lupus erythematosus [8]. The female:male ratio of systemic lupus erythematosus at age of onset or diagnosis increases with puberty from 2:1 to approximately 6:1, peaks in the fourth decade of life at 8:1, and then decreases with menopause in the sixth decade of life at 2:1 [2]. Episodes of flare-ups of systemic lupus erythematosus have been reported during periods of major sex hormone changes [9]. Abnormal metabolism of estrogens yields an excess production of 16- $\alpha$ -hydroxyestrone in patients with systemic lupus erythematosus of both

sexes [9], and low plasma androgen levels have been reported in women with active and quiescent lupus [10,11]. Studies in the NZB/W F1 hybrid mouse support a role for female hormones in the modulation of autoantibody production, development of renal disease, and death [12,13,14]. Estrogen receptors have been found on OKT8-positive lymphocytes [15].

We could not evaluate the effect of postmenopausal hormone therapy on disease activity after diagnosis because information on disease activity is not connected in a standardized manner. The benefits and risks of postmenopausal hormone therapy have been previously discussed [16]. Whether a patient should be started on this therapy is decided on an individual basis. The changes in the absolute risks imposed by this therapy on other major illnesses [17] take precedence over the increase in the relative risk for systemic lupus erythematosus.

The relation between sex steroid hormones and systemic lupus erythematosus has been studied using different research disciplines. The results of most of these studies have shown strong association, consistency, specificity, temporality, biological gradient, plausibility, and coherence and have been supported by experimental evidence [18]. Our data support these other studies, and we conclude that postmenopausal hormone therapy is causally associated with an increased risk for developing systemic lupus erythematosus in women taking hormone therapy.

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## Author and Article Information

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