Menopause, Postmenopausal Estrogen Preparations, and the Risk of Adult-Onset Asthma

A Prospective Cohort Study

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We prospectively evaluated the association of hormone replacement therapy and asthma incidence in a cohort of pre- and postmenopausal women 34 to 68 yr of age. During 582,135 person-years of follow-up between 1980 and 1990, 726 new cases of asthma were documented. Postmenopausal women who were never users of replacement hormones had a significantly lower age-adjusted risk of asthma than premenopausal women (relative risk = 0.65; 95% confidence interval [CI] = 0.46 to 0.92). Among naturally menopausal women, the age-adjusted relative risk of asthma for ever use of postmenopausal hormones was 1.49 (95% CI = 1.10 to 2.00); for current use of hormones (conjugated estrogens with or without progesterone), 1.50 (95% CI = 0.98 to 2.30); and for past use, 1.52 (95% CI = 1.08 to 2.13), compared with never use of hormones. Ever users of 10 or more years' duration had twice the age-adjusted risk of asthma compared with women who never used postmenopausal hormones (95% CI = 1.39 to 2.87). Among current users of conjugated estrogens, there was a positive dose-response demonstrated between daily dose and asthma risk (p for trend = 0.007). While confirmatory studies are warranted, these data suggest that estrogen plays a role in the pathophysiology of asthma and that long-term use and/or high doses of postmenopausal hormone therapy increase subsequent risk of asthma. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma: a prospective cohort study.

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Several lines of evidence suggest a role for hormonal factors in the etiology of asthma. With the onset of puberty, asthma incidence and frequency of hospital admissions (1) for asthma are higher among females compared with males and remain higher throughout the reproductive years (2, 3). Population-based data from Rochester, Minnesota have demonstrated that the higher incidence of asthma in adult women cannot be fully explained by diagnostic bias (2). Furthermore, in adulthood, the mean duration of hospital stay is longer for women than for men (1), suggesting that asthma may be more severe among women.

Asthma severity also has been shown to vary with short-term reproductive states, including the menstrual cycle and pregnancy. Several studies have reported that approximately one third of women with asthma experience exacerbated asthma symptoms before and/or during menstruation (4–7), and among women with premenstrual worsening, peak flow has been shown to be significantly lower when measured just before menstruation compared with midcycle (6). Other studies, however, have found no relationship between airway function (8) or responsiveness (9) and phases of the menstrual cycle. Further evidence suggests hormone levels at different phases of the menstrual cycle may differ between asthmatic and nonasthmatic women. A study assessing steroid hormone levels in asthmatic and nonasthmatic women found that at least one hormone was out of the normal range in 80% of the asthmatic women compared with 7% of the nonasthmatic women, and plasma progesterone was significantly lower in the women with asthma during the luteal phase of the menstrual cycle (10). The relation between pregnancy and asthma is unclear (11–13).

The descriptive epidemiologic data, in addition to the high prevalence of perceived worsening of asthma symptoms premenstrually, suggest that hormones may play a role in the expression of asthma in genetically susceptible women. Therefore, we investigated the relation of menopausal status, exogenous hormone use, and adult-onset asthma prospectively in a large cohort of U.S. women.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study (NHS), a prospective investigation of major disease in women, was initiated in 1976. This study has been described in detail elsewhere (14). Briefly, 121,700 female registered nurses 30 to 55 yr of age in 1976 completed a baseline questionnaire requesting information on their medical history, menopausal status, hormone use, and other reproductive and lifestyle variables. Subsequent questionnaires were completed every 2 yr, allowing participants to update their exposure

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information and report the occurrence of major illnesses. A dietary component consisting of a food frequency questionnaire was added to the study in 1980.

Postmenopausal Hormone Use

In 1976 the nurses were asked whether they had taken hormone supplements after menopause, and if so, for how long. Information on hormone use, including type taken (unopposed oral conjugated estrogen, estrogens with progestin, other estrogens, and other) was updated on subsequent questionnaires sent biennially through 1988 with explicit questions on current use and duration of use in the intervening period. Time since last use was calculated for past users and updated every 2 yr. Daily dose of conjugated estrogen (the most commonly reported hormone therapy) was asked beginning in 1980, and classified as 0.30, 0.625, and 1.25 mg and greater.

Other Risk Factors

History of oral contraceptive use was recorded on the 1976 questionnaire, and updated every 2 yr with explicit questions about current use and duration of use during the previous 2 yr.

Body mass index (BMI), a measure of relative weight, was calculated by dividing weight in kilograms by height squared in meters, and was classified as < 21, 21 to < 23, 23 to < 25, 25 to 29, and > 29. Subjects were categorized as never, past, or current cigarette smokers of 1 to 14, 15 to 24, or ≥ 25 cigarettes/d.

Study Population

Only the 93,184 women who completed a food-frequency questionnaire in 1980 were eligible for this analysis because cases of asthma were confirmed only among these participants. Since the outcome for this investigation was newly diagnosed cases of asthma, we excluded from the analysis women who reported a doctor's diagnosis of asthma, chronic bronchitis, or emphysema before 1980. In addition, women reporting a diagnosis of cancer (except nonmelanoma skin cancer), cardiovascular disease, or diabetes were excluded at baseline and throughout follow-up. Thus, at the beginning of each 2-yr interval, the population was essentially healthy. Person-time for women for whom information on hormone use was missing was excluded from the analysis (1.5%). Among current users, only those women using conjugated estrogens with or without progesterone were included in the statistical analysis (77% of person-time for current users after exclusions).

We classified women as postmenopausal from the time they reported having a natural menopause or undergoing bilateral oophorectomy. Women reporting surgical menopause without removal of both ovaries were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 yr for smokers and 56 yr for nonsmokers [15]). Self-report of menopausal status and age at menopause was highly reliable in this cohort, and among a sample of women reporting surgical menopause, for all but two women there was complete agreement on details of hysterectomy and extent of ovarian surgery between self-report and medical records (16).

In 1980, 41,202 premenopausal women and 23,035 postmenopausal women entered the analysis for the 1980–1982 period. At the beginning of each 2-yr interval, women who were subsequently classified as postmenopausal and who met the inclusion criteria entered the analysis as postmenopausal. Analyses evaluating characteristics of postmenopausal hormone use were restricted to postmenopausal women, although the relatively infrequent premenopausal use of estrogens among postmenopausal women was included when assigning person-months of exposure to duration categories. During 10 yr of follow-up from the return of the 1980 questionnaire to June 1, 1990, there were 286,440 person-years accrued among the 41,202 premenopausal women and 295,694 person-years accrued among a total of 36,094 women who were eventually considered postmenopausal.

Case Definition of Asthma

Cases of asthma for this investigation were based on the nurses' response to the following question on the 1988 and 1990 NHS questionnaires: "Have you had any of the following illnesses or procedures? Asthma, Dr. diagnosed?" We attempted to contact by mail subjects who reported a diagnosis of asthma since 1980 and who met the study inclusion criteria. Subjects were asked to complete a supplementary questionnaire eliciting information on date of diagnosis and date of first asthma symptoms, medication use, and seasonality, severity, and precipitators of asthma attacks. Nearly 97% of the nurses responded to the questionnaire. Approximately 86% of the original diagnoses of those who responded were reproduced on the supplementary questionnaire [9% of the nurses contacted denied a diagnosis of asthma, about 4% reported a diagnosis other than asthma (e.g., asthmatic bronchitis), and less than 0.5% did not provide sufficient information to confirm their diagnosis]. Of the nurses reporting a doctor's diagnosis of asthma, only 5.5% reported never taking medication specifically for asthma. For this investigation cases were defined as nurses who confirmed their NHS questionnaire report of a doctor's diagnosis of asthma on the supplementary questionnaire and who reported using asthma medication since diagnosis.

Statistical Analysis

For each participant alive and free of asthma, follow-up time equal to the number of months between the return of the 1980 questionnaire and the return of the 1982 questionnaire was assigned to each category of hormone use according to status on the 1980 questionnaire. Similarly, for each 2-yr interval, additional months of follow-up were assigned until June 1, 1990, according to status at the beginning of the interval. Thus, the current use category includes past users of, at most, 2 yr duration. For participants who reported a diagnosis of asthma or who died, follow-up time accumulated until the date of diagnosis reported on the supplementary questionnaire or the date of death. For participants reporting a diagnosis of cardiovascular disease, cancer, or diabetes, follow-up time accumulated until the beginning of the interval during which the disease was reported.

The relative risk was used as the measure of association and was calculated by dividing the incidence rate for each category of hormone use by the corresponding rate in the never users and summarizing across age in 3-yr categories (the estimates of effect were similar when adjusted for age in 1-yr categories, but the confidence intervals were slightly wider). The Mantel extension test (17) was performed to test for linear trend across ordered categories of duration of hormone use and hormone dose. Relative risks were adjusted simultaneously for age, smoking status, BMI, and type of menopause, which were updated every 2 yr, using proportional hazards models (18, 19). In addition, proportional hazards models were used initially among both the pre- and postmenopausal women to evaluate the association of menopausal status to asthma stratified by ever use of hormones among postmenopausal women. Relative risk estimates adjusted for age only are presented in the tables when similar estimates were obtained from the multivariate models. Ninety-five percent confidence intervals were calculated for each relative risk. All p values are two-tailed.

RESULTS

Among the 23,035 women who were postmenopausal in 1980, current use of postmenopausal hormones accounted for 10% of follow-up time among naturally menopausal women and 39% of follow-up time among surgically menopausal women, while former use accounted for 21% and 39%, respectively. The age-standardized exposure status of women by hormonal status at baseline in 1980 is presented in Table 1. Current users of hormones were more likely to be lean and to have used oral contraceptives in the past.

During 10 yr of follow-up we documented 404 new cases of asthma among premenopausal women and 322 cases among postmenopausal women. Incidence of asthma without regard to menopausal status was inversely related to age: in women under 50 yr of age the incidence rate was approximately 1.4 cases per 1,000 person-years and decreased to approximately 1.1/1,000 in women 50 yr and older. The incidence rates did not vary substantially within age groups.

In analyses adjusted for age, BMI, and smoking status, and stratified by hormone use (Table 2), women who were naturally menopausal and reported never using postmenopausal hormones had a significantly lower risk of asthma compared with premenopausal women (relative risk [RR] = 0.65; 95% confidence interval [CI] = 0.46 to 0.92). A weaker inverse relation was observed

TABLE 1

DISTRIBUTION OF SEVERAL CHARACTERISTICS IN 1980 AMONG 23,035 POSTMENOPAUSAL WOMEN IN NHS, ACCORDING TO POSTMENOPAUSAL HORMONE USE WITH STANDARDIZATION FOR AGE*

	Postmenopausal Hormone Use		
	Never (%) (*n* = 12,630)	Past (%) (*n* = 6,462)	Current (%) (*n* = 3,943)
Age category			
30–34	< 1	1	< 1
35–39	1	5	1
40–44	2	10	3
45–49	12	20	11
50–54	42	30	30
55–59	44	35	55
60–64	< 1	< 1	< 1
Smoking status			
Never	43	40	43
Current	31	32	29
Past	26	28	28
Body mass index†			
< 21	16	16	21
22 – < 23	21	23	26
23 – < 25	22	23	22
25 – < 29	24	24	22
⩾ 29	16	14	9
Type of menopause‡			
Natural	86	30	52
Bilateral oophorectomy	9	58	39
Past use of oral contraceptives	26	31	34

* All variables except age were standardized to the age distribution of the entire cohort in 1980.

† Body mass index was calculated by dividing weight in kilograms by the square of height in meters.

‡ Excludes women who underwent hysterectomy with or with unilateral oophorectomy.

for naturally menopausal women who reported ever use of hormones compared with premenopausal women (RR = 0.77; CI = 0.52 to 1.13). The study had little power to detect differences in risk for asthma between surgically menopausal women who never took hormones and premenopausal women; however, as a group, women with both ovaries removed had a lower risk for asthma.

Among naturally menopausal women, age at menopause was examined within age at diagnosis groups to determine whether cumulative exposure to endogenous estrogens as represented by increasing age at menopause was related to risk of asthma. Although limited in statistical power, the results showed no clear trends. Similarly, holding age at diagnosis constant, no notable relation was observed with time since menopause, suggesting that the effect of menopause on asthma risk is acute without a dose-response (age-adjusted incidence rates for time since menopause: < 5 yr = 0.71/1,000 person-years, 5–10 yr = 0.98/1,000, and > 10 yr = 0.77/1,000).

In naturally menopausal women, the age-adjusted relative risk of asthma for women who reported ever using postmenopausal hormones was 1.49 (CI = 1.10 to 2.00) compared with women who reported never using hormones. The age-adjusted relative risk for current hormone users was 1.50 (CI = 0.98 to 2.30), and for past users was 1.52 (CI = 1.08 to 2.13) compared with never users (Table 3). Risk associated with hormone use was substantially diminished (p for interaction = 0.27) among surgically menopausal women: the relative risk for hormone use was 1.14 (CI = 0.71 to 1.83) for current users and 1.03 (CI = 0.65 to 1.64) for past users compared with women who never used hormones.

Risk of asthma appeared positively associated with duration of use in both current and past users of hormones, although among hormone users alone, the trends were not statistically significant (Table 4). Ever hormone users of 10 or more yr duration had twice the age-adjusted risk of asthma than women who never used hormones (CI = 1.39 to 2.87). Risk among past users appeared to remain elevated for several years after stopping hormone use (age-adjusted RR [CI] of time since quitting compared with current users: < 3 yr = 1.13 [0.60 to 2.13], 3–6 yr = 1.12 [0.57 to 2.18], > 6 yr = 0.75 [0.41 to 1.39]). Estimates of relative risk for asthma were similar for current users of conjugated estrogens with (58%) and without progesterone (42%). Among naturally menopausal women, the relative risk of asthma among current users of conjugated estrogens only was 1.42 (CI = 0.80 to 2.53) and among combined estrogen and progesterone users was 1.50 (CI = 0.81 to 2.79) compared with never users of hormones, with adjustment for age, BMI, and smoking status. Furthermore, current dose of conjugated estrogens was positively related to age-adjusted risk of asthma in a dose-response fashion (p for trend = 0.007) (Figure).

Because of the relatively small number of women who were currently using oral contraceptives during the study period, we assessed only the relationship of past use of oral contraceptives and risk of asthma among both pre- and postmenopausal women. Past users of oral contraceptives had a modest but significantly elevated age-adjusted risk of asthma compared with women who never used oral contraceptives (RR = 1.25; CI = 1.07 to 1.47). There were no notable trends with duration or time since last use of oral contraceptives.

Current hormone users were more likely to have previously used oral contraceptives. Among naturally menopausal women, with simultaneous inclusion of past use of oral contraceptives and postmenopausal hormones in the model, the relative risk of asthma for both past oral contraceptive use (1.57; CI = 1.16 to 2.12) and postmenopausal hormone use (for current use, 1.38; 0.88 to 2.15, and for past use, 1.41; 1.00 to 1.99) remained elevated with adjustment for age, BMI, and smoking status. Previous use of oral contraceptives did not modify the relation between ever use of postmenopausal hormones and asthma (p for interaction = 0.84).

Because of increased physician contact, women receiving hormone therapy may have been more likely to be diagnosed with asthma than women not taking hormones. To address this pos-

TABLE 2

RELATIVE RISK FOR MENOPAUSAL STATUS AND ASTHMA* STRATIFIED BY POSTMENOPAUSAL HORMONE USE (NEVER OR EVER USE) AND ADJUSTED FOR AGE, BODY MASS INDEX, AND SMOKING STATUS (NURSES' HEALTH STUDY, 1980–90)

	Never Users of Hormones			Ever Users of Hormones		
Menopausal Status	Cases	Person-Time	Relative Risk (95% CI)	Cases	Person-Time	Relative Risk (95% CI)
Premenopausal	404	286,440	1.0	404	286,440	1.0
Natural menopause	116	139,347	0.65 (0.46–0.92)	75	61,490	0.77 (0.52–1.13)
Bilateral oophorectomy	9	9,827	0.66 (0.33–1.31)	72	54,718	0.83 (0.60–1.14)

* Women who underwent hysterectomy alone or with unilateral oophrectomy are not included in this table.

TABLE 3

RELATIVE RISK (95% CONFIDENCE INTERVAL) FOR POSTMENOPAUSAL HORMONE USE AND ASTHMA, STRATIFIED BY TYPE OF MENOPAUSE, ASSESSED IN 1980 AND UPDATED EVERY 2 YR

	Never	Current	Past
Natural menopause:			
No. of cases	116	25	50
No. of person-years	139,347	20,095	41,395
Relative risk	1.0	1.50	1.52
(95% CI)		(0.98–2.30)	(1.08–2.13)
Surgical menopause			
No. of cases	28	55	48
No. of person-years	21,482	36,852	36,523
Relative risk	1.0	1.14	1.03
(95% CI)		(0.71–1.83)	(0.65–1.64)

sibility, we repeated the analysis restricted to naturally menopausal women who reported a physician or clinic visit in 1978 (61% of the study population). Because of the reduced number of cases, current and past hormone users were combined. The results were only slightly attenuated. The age-adjusted relative risk of asthma for ever hormone users in this restricted group was 1.32 (CI = 0.92 to 1.90) compared with women who never used hormones (in the original analysis RR = 1.49; CI = 1.10 to 2.00). Repeating the original analysis with a stricter case definition (asthmatic subjects with medication use within the past week) among naturally menopausal women, the age-adjusted relative risk for current use was 2.17 (CI = 1.36 to 3.46) and for past use was 1.36 (CI = 0.87 to 2.13) compared with never use.

DISCUSSION

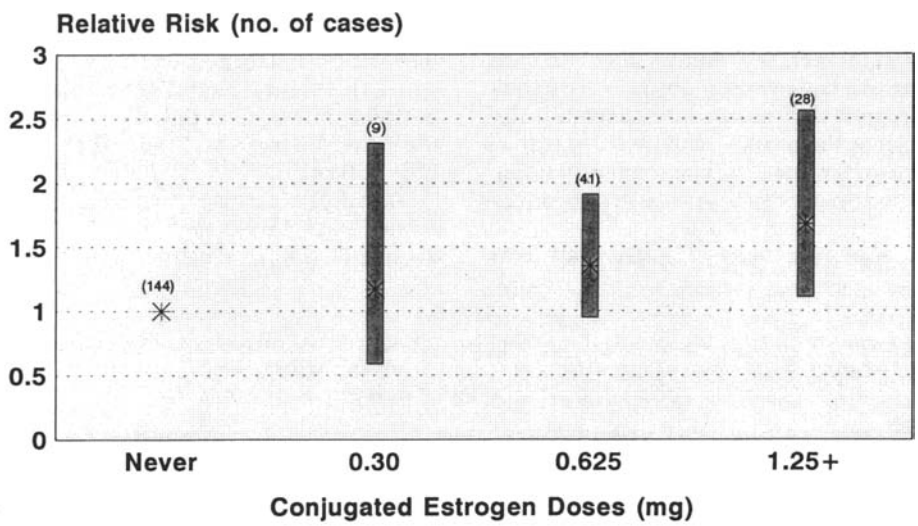
In this prospective study, age-adjusted incidence of asthma was lower in postmenopausal women than in premenopausal women. The magnitude of this difference was greater among postmenopausal women who reported never using hormones compared with women reporting current or past use, suggesting that some of the benefit of menopause is lost with hormone replacement therapy. Both past and current postmenopausal hormone use was associated with an increased risk of asthma among naturally menopausal women. Asthma risk was highest in users of long duration and positively associated with current dose of conjugated estrogens. In addition, past use of oral contraceptives was independently associated with a modestly increased risk of asthma.

The prospective design of this study precludes the possibility that these results are explained by recall bias since information on hormone use was collected before diagnosis of asthma. While postmenopausal hormone use was self-reported in this investigation, misclassification should be minimal because the study subjects were registered nurses with a demonstrated interest in medical research. Furthermore, any random misclassification in hormone use would lead to an underestimation of the true association.

Another potential source of bias is the possibility that increased opportunity for diagnosis might occur among women using hormones since they must be under a physician's care to receive a prescription. We attempted to address this concern by performing the original analysis in women who had reported at least one physician or clinic visit in 1978, a group that was more likely to be in regular contact with a health care provider. The relative risk for ever use of hormones was attenuated only slightly. In fact, because the subjects are nurses, opportunity for asthma diagnosis in the presence of symptoms should be relatively uniform. Repeating the original analysis with a stricter case definition (asthmatic subjects reporting medication use within the past week) reflecting active asthma resulted in a stronger relationship between current use of postmenopausal hormones and risk of asthma. Because of the severity of disease in these cases, it is extremely improbable that greater access to medical care would have affected their opportunity for diagnosis.

The observation of a greater increase in asthma risk with postmenopausal hormone use among naturally than among surgically menopausal women is puzzling, although the difference was

Figure 1. Age-adjusted relative risk (95% confidence interval) for dose of conjugated estrogens and asthma among current users



Test for trend includes never users; p=0.007.

Figure. Dose of conjugated estrogen among women with new onset asthma, NHS, current use (relative risk, age-adjusted).

TABLE 4

AGE-ADJUSTED RELATIVE RISK FOR DURATION OF POSTMENOPAUSAL HORMONE USE AND ASTHMA

Duration of Hormone Use	Cases	Person-Years	Relative Risk (95% Confidence Interval)
Current use (yr)			
0	144	160,830	1.0 (Referent)
< 1	15	10,400	1.56 (0.92–2.65)
2–5	19	15,863	1.25 (0.76–2.05)
6–10	19	15,165	1.34 (0.82–2.19)
> 10	24	14,321	1.87 (1.21–2.89)
			χ, trend* = 0.59 (p = 0.56)
Past use			
0	144	160,830	1.0 (Referent)
< 1	36	32,592	1.23 (0.85–1.77)
2–5	29	21,310	1.52 (1.02–2.28)
6–10	18	13,609	1.51 (0.93–2.47)
> 10	13	6,578	2.28 (1.30–4.00)
			χ, trend* = 1.51 (p = 0.13)
Ever use			
0	144	160,830	1.0 (Referent)
< 1	51	42,992	1.32 (0.96–1.82)
2–5	48	37,173	1.40 (1.00–1.95)
6–10	37	28,774	1.42 (0.98–2.05)
> 10	37	20,899	2.00 (1.39–2.87)
			χ, trend* = 1.57 (p = 0.12)

* Test for trend does not include never users of hormones.

not statistically significant and may have been due to chance variation is risk estimates. In addition, the reference group for the comparison among surgically menopausal women was dominated by hysterectomized women who, in general, had a higher incidence of asthma than oophorectomized women. Finally, confounding by indication for estrogen use, whereby women at high risk of asthma are selectively prescribed oral contraceptives or postmenopausal hormones, cannot be ruled out, although a medical explanation is not readily apparent.

Bias due to unmeasured confounders cannot be excluded in observational studies in this case, since women using hormone replacement therapy (HRT) are likely to be different in other characteristics than women not using HRT. There is reason to believe, however, that these differences are less pronounced in the NHS than in the general population. When compared with women not using HRT, women using HRT had only a slightly healthier lifestyle in the NHS (20), certainly not enough to explain the 50% increase in risk observed in the present study. In addition, since few risk factors have been identified for adult-onset asthma, the importance of these small differences are unclear. Adjustment for the most conspicuous confounders, smoking status and BMI, did not change the estimates of relative risk. The results remained the same with further adjustment for oral contraceptive use, vitamin E intake (found to be associated with asthma in a previous study in this cohort), and area of residence.

Results of the analyses regarding menopausal status seem to indicate that the possible effect of estrogen in the pathophysiology of asthma is acute rather than cumulative or dose-responsive. Comparing time since menopause among women of the same age at asthma diagnosis showed no clear trends, although statistical power was limited. In contrast, analyses involving exogenous hormone use demonstrated risk estimates for past and current use that were of similar magnitude, implying that sensitization occurs over a long period of time, placing past as well as current hormone users of long duration at higher risk of asthma. Alternatively, the residual impact of higher doses of postmenopausal hormones used in the past may be comparable to the short-term effects of recent use. Nevertheless, asthma risk was positively, though not significantly, associated with duration of hormone use, suggesting further that cumulative exposure to exogenous hormones may be important.

A recent case report documented the occurrence of increased airflow limitation associated with postmenopausal hormone use that subsided with discontinuation and resumed with readministration (21), however, there have been no observational studies that have assessed the relation of postmenopausal hormone use and new-onset asthma. Estradiol has been shown to increase acetylcholine (22) and cholinesterase activity (23) in animals and accelerate the release of secretory material from epithelial cells in the trachea (24). In addition, estrogen and progesterone influence free cortisol levels: estrogen by enhancing production of corticosteroid binding globulin and progesterone by competition with cortisol for binding sites. Estrogen and progesterone also have been demonstrated to modify beta-adrenergic receptor site density in the rabbit lung with estrogen increasing and progesterone decreasing the number of sites (25). Lastly, high levels of estrogen may modify relative levels of PGF_2 and PGE_2 (26). In light of our observations regarding menopause and exogenous hormone use and asthma risk, more basic research on how sex steroid hormones affect the lung appears warranted.

The literature on oral contraceptive use and asthma is equally scant. A case report published in the late 1960s notes the development of bronchial symptoms in a woman who began taking oral contraceptives 4 yr earlier, which subsided after discontinuation (27). More recently, a clinical study of seven asthmatic women using oral contraceptives found no difference in airway responsiveness measured within 1 wk of completing a 21-d course and airway responsiveness measured after the start of menstruation but before restarting oral contraceptives (28). On the contrary, we found an increased risk of asthma among women who previously used oral contraceptives compared with women who never used oral contraceptives that was independent of present or past use of postmenopausal hormones.

The congruity of several observations from this study contribute to the plausibility of an adverse role of postmenopausal estrogen preparations in the development of adult-onset asthma in women. Firstly, postmenopausal women had a significantly lower risk of asthma than premenopausal women of the same age, with postmenopausal women on hormone therapy being at moderately greater risk compared with those women that did not receive such therapy. Secondly, dose was positively associated with asthma risk, and the highest risk of asthma was found among women taking hormones for 10 or more yr duration. Finally, when the original analysis was repeated with a stricter case definition (asthma with medication use in the past week), the association of current use of hormones and asthma became stronger.

These data provide preliminary evidence that in some postmenopausal women, long-term use of high doses of estrogen may be associated with a moderately increased risk of asthma; however, confounding by indication for estrogen use cannot be ruled out. In light of these results, a recent recommendation suggesting that HRT might be beneficial in counteracting decreases in bone density resulting from long-term use of steroids for the treatment of asthma should be reexamined (29). Given the prevalence of exogenous hormone use and the severity of asthma in the elderly (30, 31), this association deserves further examination and confirmation in other studies. In particular, additional studies are needed to identify factors that better predict which women will develop asthma in response to hormone use.

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