DECREASED RISK OF FRACTURES OF THE HIP AND LOWER FOREARM WITH POSTMENOPAUSAL USE OF ESTROGEN

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Abstract We interviewed 327 women who had been 50 to 74 years of age when treated for fracture of the hip or lower forearm, to determine their use (or lack of use) of estrogen preparations. Their responses were compared with those in a random sample of 567 women who were of similar age and from the same region. The risk of fracture was 50 to 60 per cent lower in women who had used these drugs for six years or longer than in women who had not used them (95 per cent confidence interval of relative risk, 0.3 to 0.6); those using them for shorter periods received less benefit, if any. A decreased risk of fracture was clearly evident only in women still taking estrogens and evident at either common daily dose (0.625 and 1.25 mg).

In conjunction with the finding that estrogens can retard the development of osteoporosis in postmenopausal women, our data argue that lowering of the risk of hip and forearm fractures must be weighed as a benefit of long-term estrogen use. (N Engl J Med. 1980; 303:1195-8.)

DURING the past several years, the use of estrogen preparations by postmenopausal women has been shown to retard the age-related decrease in bone density.[1-3] However, loss of bone density itself is of little clinical relevance; it is important primarily to the extent that it predisposes bone to an increased likelihood of fracture. Although one would expect that the presence of relatively dense bones as a result of estrogen use would prevent some fractures, the magnitude of this prevention has not been well documented. Since a woman's decision to use estrogens involves weighing this benefit and others against the risks involved, knowledge of the magnitude of estrogen-related reduction in fracture risk has a great deal of practical value.

The most common sites of fracture among postmenopausal white women are the vertebras, forearm, and hip.[4] The incidence of these three types of fracture is much higher than the incidence among men of similar ages, whereas in younger adults there is little difference in incidence between the sexes. This fact suggests that the prevention of vertebral, forearm, and hip fractures, more than that of other types, may occur if estrogen is continued after the menopause.

Our study was designed to determine how commonly women who had had two of these types of fracture — forearm and hip — had used estrogen preparations, and to what extent they differed in this respect from a sample of other women from the general population.

METHODS

During 1978-1979, arrangements were made with 59 Seattle-area (King County) orthopedic surgeons to identify patients in their practices who had had a fracture of the hip (femoral head to lesser trochanter) or lower forearm. Patients eligible for the study were white women whose injury had occurred during the preceding two years and who were 50 to 74 years of age at that time. In the patients of some surgeons (primarily those physicians contacted in 1978) case identification was continued prospectively for an additional year.

Although the selection of physicians was designed to approximate the geographic distribution of orthopedic care in King County, the selection was not strictly at random and thus is not necessarily representative of the approximately 95 orthopedic surgeons who were practicing in the county at that time. Three orthopedists declined to participate; the remainder were not approached because of the study's resource limitations.

The actual method of case identification varied from practice to practice; the two most common sources were computerized billing records and hospital-discharge indexes. Only subjects with hip fractures were included in the practices in which outpatient diagnoses could not be ascertained, since only a few women with forearm fractures needed hospitalization. Thus, the ratio of fractures of the forearm to fractures of the hip in these subjects ($\approx$1.3:1) is well below that which occurs in the general population of women 50 to 74 years of age. Women who sought care for vertebral fractures from the orthopedists in the study were not identified, because we thought that these women would make up a small and probably unrepresentative sample of all those who had had such fractures.

Excluded from the study were women who were residents in an institution (e.g., a nursing home) at the time of the injury, who were not residents of King County, who had had multiple fractures in a single accident, or who had a diagnosis of pathologic fracture.

Twenty-four of 385 potential subjects had died before the start of the study. We attempted to contact the remainder, and obtained an interview with 327 (91 per cent). The interview dealt with experiences and characteristics relating to endogenous hormone levels (e.g., history of pregnancy and lactation, menopausal status, and weight) and with the use of estrogen-containing preparations. When the interview was conducted in person (87 per cent of interviews), the interviewer showed a color display of these preparations to facilitate the subject's recall. No information concerning diet was obtained.

Our control subjects were white women 50 to 74 years of age who had an interview during household surveys of King County in 1976, 1977, and 1979 that was identical to the interview of the cases. Standard area-sampling methods were used to identify these women. In the 1976 survey, we divided the county into 133 contiguous strata of approximately equal populations and randomly selected two sampling units (averaging about four households) from each stratum. In the 1979 survey, we selected a sampling unit adjacent to one of the first two chosen in 1976. In the 1977 survey, we used a greater number of strata (200) and a smaller average size of sampling unit (two households), but in other respects this survey was similar in design to the others. Overall, interviews were obtained from 576 of the 626 controls identified (92 per cent); 541 interviews (94 per cent) were conducted in person.

For the cases, information on use of estrogens until the date of the fracture was tabulated. For the controls, use until the date of the interview was tabulated, since among controls the distribution of

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dates of interviews corresponded closely to the distribution of dates of fracture among cases.

The reasons for use of estrogens were not asked; thus, the women for whom estrogens had been prescribed for osteoporosis could not be identified. We decided, arbitrarily, that the likelihood that estrogens were prescribed for osteoporosis would be relatively high if estrogen use began at age 60 or later, and accordingly excluded subjects who met this criterion (three cases and eight controls) from further analysis. Finally, we excluded four cases and one control who believed that they might have used estrogens in the past but who could provide no details about which drug they had taken or how long they had taken it.

This study directly measured the relative proportion of estrogen users and nonusers among cases and controls, i.e., the relative odds of estrogen use. Because the incidence of fracture in users as related to that in nonusers (i.e., relative risk) is accurately estimated by the relative odds, and because the concept of relative incidence has greater intuitive meaning, the results are expressed in these terms.

Results

To place in perspective any differences between cases and controls in the use of estrogens, we compared the two groups for certain demographic characteristics (Table 1). Nearly 97 per cent of the women in each group had been married. On the basis of an indirect measure of income (1970 median income of census tract of residence), cases were slightly more affluent than controls. Income did have a moderate relation to estrogen use (greater likelihood of use among women with higher incomes), but control of this variable had no meaningful effect on the size of the association between estrogen use and fractures. Paradoxically, the cases reported a lower average level of education than did controls but, since there was no correlation between education and estrogen use, this variable proved not to be confounding. On the other hand, a somewhat higher proportion of controls than cases had undergone hysterectomy (with or without bilateral oophorectomy). Because prior hysterectomy was related strongly to the likelihood of estrogen use, we controlled for its effect in all subsequent analyses.

Table 1. Selected Characteristics of 320 Cases with Fractures and 567 Controls.

Characteristic	Cases *	Controls
	per cent	
Ever married	97	97
Income >$12,114 †	46	40
Education (yr)		
<12	27	20
12	39	35
>12	34	45
Intact uterus	70	60
Prior hysterectomy		
With unilateral oophorectomy	15	21
With bilateral oophorectomy	13	16
Status of ovaries unknown	3	3

*Values are adjusted according to the age distribution of controls. Fracture of forearm occurred in 56 per cent of cases, and fracture of hip in 44 per cent.

†1970 median family income of census tract of residence.

Table 2. Menopausal Estrogen Use among 320 Cases with Fracture and among 567 Controls, According to Duration of Use.

Duration of Use	Cases	Controls	Relative Risk *	95 per Cent Confidence Interval †
yr	*per cent*			
No use ‡	66	48	1.0	—
1–2	10	9	0.84	0.51–1.4
3–5	9	10	0.89	0.54–1.4
6–9	5	12	0.38	0.22–0.66
⩾10	11	21	0.46	0.30–0.69

*Standardized for age group (50 to 59, 60 to 69, and 70 to 74 years), history of hysterectomy, and current use versus past use of estrogens, by the method of Mantel and Haenszel.[5]

†Approximate values, by the method of Miettinen.[6]

‡Includes women using estrogens for less than one year.

Cases who had had hip fractures and those who had had forearm fractures had identical patterns of estrogen use, and they are analyzed as one group hereafter. The distribution of duration of their estrogen use and that of the controls is shown in Table 2. The estimated risk of fracture among users of estrogen for five years or less is slightly lower than that among nonusers, but the numbers are too small to determine whether the difference occurred by chance. Beyond the point of five years, however, the lowered risk is clear; for these durations we estimate the likelihood of fracture in an estrogen user to have been only 40 to 50 per cent of that of a nonuser. The negative association was present in each of the age groups studied (50 to 59, 60 to 69, and 70 to 74 years), and in either group of women regardless of hysterectomy status.

The relation between past use of estrogens and occurrence of fracture appeared to be weaker than that for present use (Table 3). However, the relatively small number of women who had discontinued estrogens before the study precludes any precise assessment about how much, if at all, their risk of fracture remained below that of women who had not used estrogens.

Each woman's average dose of conjugated estrogens (or equivalent dose of other estrogens) was computed. Episodes in which injections were received or in which the preparation was unknown were excluded. If duration of exposure is controlled for, the reduction in risk of fracture was identical in users of less than 1 mg per day (typically 0.625 mg) and in users of higher doses (typically 1.25 mg per day).

If use of estrogens after menopause does provide protection against hip and forearm fractures, its effect might be expected to be most apparent in accidents involving relatively little trauma. Our measurement of the degree of trauma was a crude one, i.e., a description by the subject of the circumstances of her accident. We separated the accidents into two groups: those in which there was no greater trauma than that resulting from a fall from standing height (258 cases), and more serious accidents, e.g., falling down stairs (62 cases). The two groups had a nearly identical pat-

Table 3. Menopausal Estrogen Use among 320 Cases with Fracture and among 567 Controls, According to Time since Latest Use.

Time Since Latest Use	Cases	Controls	Relative Risk *	95 per Cent Confidence Interval †
yr	*per cent*			
No use	66	48	1.0	—
≥6	10	9	0.77	0.48–1.2
3–5	4	4	1.0	0.50–2.0
1–2	6	7	0.74	0.41–1.3
Current use	14	32	0.43	0.30–0.63

*Standardized for age group (50 to 59, 60 to 69, and 70 to 74 years), history of hysterectomy, and duration of estrogen use (none, one to five years, and six years or more), by the method of Mantel and Haenszel.[5]

†Approximate values, by the method of Miettinen.[6]

tern of estrogen use; the decreased risk thus appeared to apply at both levels of trauma.

One possible bias in our method of analysis is the comparison of case interviews without information on estrogen use during the interval between fracture and interview (one year on the average) with control interviews that included such information. Our reason for choosing this method was to keep case and control histories comparable in terms of calendar time, since on the average the controls were interviewed one year before the cases, and since there were sharp changes in the prevalence of estrogen use in King County during 1975-1979. However, when the data were reanalyzed without consideration of the past year's estrogen use among controls as well (to correspond to the average interval between fracture and interview for cases), the estimates of relative risk were changed only in the second decimal place.

Discussion

Limitations of the Data

Women in our control group were not asked about previous forearm or hip fractures. On the basis of incidence rates in similar populations, one would expect that approximately five controls had had a forearm fracture, and two a hip fracture, in the two to three years during which fractures had occurred in the cases. Because these control subjects were not identified and excluded, we underestimated very slightly the reduction in fracture risk associated with estrogen use.

Of possibly greater concern is the lack of data on trauma to which the bones of cases and controls were subjected and of data regarding determinants of bone density other than estrogen use (e.g., diet, vitamin D intake, and parathyroid hormone levels). We made the assumption that estrogen users and nonusers did not differ in any important way with respect to any of the above variables. The fact that the risk reduction that we observed was not universal among estrogen users but largely confined to those with longstanding use or recent use (or both) suggests that the assumption was probably valid.

Does Estrogen Use Lower the Risk of Forearm and Hip Fractures in Postmenopausal Women?

Virtually all the available evidence argues that the answer to this question is "Yes."

Postmenopausal women randomly assigned to estrogen treatment in three clinical trials did not have the loss of bone density characteristic of women assigned to a placebo.[1-3] Ample laboratory and clinical data exist to account for this finding.[7]

The observation that the risk of hip and forearm fracture varied according to the particular pattern of estrogen use — lowest risk in women who had taken the drugs for several years or who were still taking them at the time of the study — is consistent with what would have been predicted from the clinical trials of estrogen treatment in postmenopausal women. In those studies the difference in bone density between treated and untreated women grew with duration of treatment[1,2] and, once treatment was discontinued, disappeared within several years.[8]

We estimated no greater decrease in fracture risk for users of 1.25 mg per day of conjugated estrogens than for users of 0.625 mg per day. However, since daily doses both above and below 1 mg have been found adequate to maintain bone density,[1-3] this result is not surprising.

An earlier case-control study of hip and forearm fractures in postmenopausal women[9] found a relative deficit of estrogen use among cases of about the same magnitude as did the present study.

To What Extent Can a Woman's Risk of Fracture Be Reduced by the Use of Estrogens?

The likelihood of a postmenopausal woman's breaking her forearm or hip, as a function of age, is shown in Table 4. If long-term estrogen use is assumed to lower the rate by 60 per cent (Table 2), a woman can expect to improve her chances by 0.3 to 3.0 per 1000 per year, depending on the type of fracture and her age. In terms of incidence itself, these projected reductions in risk are quantitatively smaller

Table 4. Estimated Incidence of Fracture of the Lower Forearm and Hip in Postmenopausal Women, According to Age Group and Use of Estrogens.

Fracture	Age Group		
	50–59	60–69	70–74
	annual rate/ 1000 women[4,10,11]		
Lower forearm			
No estrogen use	3.0	5.0	5.0
Estrogen use *	1.2	2.0	2.0
Difference	1.8	3.0	3.0
Hip			
No estrogen use	0.5	1.5	5.0
Estrogen use *	0.2	0.6	2.0
Difference	0.3	0.9	3.0

*Current use of six years' duration or longer. Rate was obtained by multiplying rate in women not using estrogens by relative risk of 0.4.

than the added incidence (5 to 25 per thousand per year[12]) of endometrial cancer in such a woman if her uterus is intact. On the other hand, the other potentially important skeletal benefit, reduction in the incidence of vertebral fractures, has not been taken into account; no data exist to determine the occurrence or magnitude of such a reduction. Until these data and other data regarding benefits to health resulting from estrogen use become available, the decision to use these drugs on a long-term basis will remain an uncertain one for many women.

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THE APPEARANCE OF CELL-BOUND IgE IN RESPIRATORY-TRACT EPITHELIUM AFTER RESPIRATORY-SYNCYTIAL-VIRUS INFECTION

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Abstract We studied the appearance of IgE in the respiratory tract in 42 infants and young children with various forms of respiratory illness after infection by respiratory syncytial virus (RSV). IgE was bound to exfoliated nasopharyngeal epithelial cells in most patients with RSV infection during the acute phase of infection, regardless of the form of illness. However, the continued presence of cell-bound IgE was more common in patients with RSV-induced bronchiolitis or asthma than in patients with mild upper-respiratory-tract illness or pneumonia due to RSV. Persistence of IgE was also apparently related to the incidence of previous episodes of wheezing in patients or their families.

The production of IgE and the subsequent release of chemical mediators of bronchospasm may contribute to the pathogenesis of acute illness due to RSV; persistence of IgE in the respiratory tract may explain the recurrent episodes of wheezing that occur in many patients after RSV-induced bronchiolitis. (N Engl J Med. 1980; 303:1198-1202.)

THE association of viral infections with acute episodes of wheezing in patients with and without previous episodes of bronchiolitis or asthma is well recognized.[1,2] Respiratory syncytial virus (RSV) is the infectious agent most commonly associated with episodes of acute wheezing in infants and young children.[1-3] Little information is available on the mechanism by which infections with RSV and other viruses may result in wheezing. Previous studies have failed to demonstrate a consistent IgE response in serum in patients with bronchiolitis caused by RSV,[4] although brief reports have described transient increases in total IgE in serum after infection with several other agents.[5,6] We undertook this study to determine whether infection with RSV results in the appearance of IgE in the respiratory tract — the site of initial viral replication as well as the target organ of the disease. The results demonstrate the appearance of IgE bound to exfoliated nasopharyngeal epithelial cells (NPEC's) in the first few days of illness in most patients with RSV infection. Cell-bound IgE persists for longer periods in patients with bronchiolitis or asthma due to RSV than in patients with upper-respiratory-tract illness alone or in patients with pneumonia due to RSV.

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Methods

Study Population

The patient population consisted of 42 children less than one year of age, who had documented RSV infection and were consecutively recruited from our ongoing study of respiratory illness in childhood. In this study, normal children with croup, pneumonia, bronchiolitis, or asthma are seen during each episode of respiratory illness. RSV infection was documented by identification of viral antigen in nasopharyngeal secretions by indirect immunofluorescence,[7] and by recovery of virus in tissue culture.[8] Six patients were classified as having upper-respiratory-tract illness, nine patients as