Issues concerning the use of hormone replacement therapy and risk of fracture: a population-based, nested case-control study

Giovanni Corrao, Antonella Zambon, Federica Nicotra, Valentino Conti, Rossella E. Nappi^{1,2} & Luca Merlini³

Unit of Biostatistics and Epidemiology, Department of Statistics; University of Milan-Bicocca, Milan, ¹Research Center for Reproductive Medicine, Department of Morphological, Eidological and Clinical Sciences, University of Pavia, Pavia, ²Endocrinology and Internal Medicine Unit, Section of Gynaecological Endocrinology, IRCCS Maugeri Foundation, University of Pavia, Pavia and ³Operative Unit of Territorial Health Services, Region Lombardia, Milan, Italy

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Several studies have consistently shown that hormone replacement therapy (HRT) can reduce the risk of fracture.
- The questions that are still controversial include the duration of treatment needed, the duration of the protective effect after treatment is stopped, and the influence of age at which treatment is initiated.

WHAT THIS STUDY ADDS

- Our findings suggest that HRT should be continued for long periods to achieve optimal protection from fracture.
- The fracture reducing potential of HRT seems to disappear after a few months without treatment and might mainly act in women who begin therapy at an older age.

Correspondence

Professor Giovanni Corrao, Dipartimento di Statistica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi 8, Edificio U7, 20126 Milano, Italy.

Tel: + 39 02 6448 5854

Fax: + 39 02 6448 5899

E-mail: giovanni.corrao@unimib.it

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AIMS

To investigate the effect of duration, how recently it has been used, and age at start of hormone replacement therapy (HRT) and the risk of bone fracture.

METHODS

A population-based, nested case-control study was conducted in Lombardia, Northern Italy. The 78 294 women aged 45–75 years who received at least one HRT prescription during 1998–2000 were followed until 2005. Cases were women who experienced bone fracture during follow-up. Up to six controls were randomly selected for each case from the cohort after matching for age and date of cohort entry. The odds ratio of fracture associated with the use of HRT was estimated by conditional logistic regression.

RESULTS

One thousand one hundred and seventy-four cases and 6760 controls were included. Compared with women who took HRT for less than 2 months, those who were treated for more than 20 months had an odds ratio (OR) of 0.80 (95% confidence interval 0.65, 0.99). This risk reduction was still significant among current HRT users (OR 0.71, 95% CI 0.55, 0.90) and in women who began therapy at the age of 55–65 years (OR 0.63, 95% CI 0.42, 0.94) or 65–75 years (OR 0.56, 95% CI 0.32, 0.99). There was no statistical evidence of a protective effect for women who had stopped treatment more than 6 months previously or those who began HRT at the age of 45–55 years.

CONCLUSIONS

HRT should be continued for long periods to achieve an optimal protection from fracture. The fracture reducing potential of HRT seems to disappear after a few months without treatment and might mainly act in women who begin therapy at older age.

Introduction

Menopause is accompanied by accelerated bone loss [1,2], and increasing incidence of fractures [3–5]. Several studies have shown that hormone replacement therapy (HRT) can reduce bone loss [6–10], increase bone mineral density [11–15], and decrease the risk of fracture [15–31]. However, the duration of treatment needed and of the protective effect after treatment is stopped, and the influence of age at which treatment is initiated, are still controversial [9, 17, 21, 24, 32]. We carried out a large, population based, nested case-control study to investigate these issues.

Methods

The data used for this study were obtained from the health services database of Lombardia. Lombardia is one of 20 Regions in Italy, with a population of about 9 million inhabitants (about 16% of the population of Italy). The population is entirely covered by the National Health Service (NHS), which has administered this program since 1997. It utilizes an automated system of databases on the use of health services including demographic and administrative data, hospital discharge and outpatient prescription drug benefits. Information is recorded for the NHS and can be linked for each individual using a unique personal identification code.

Procedures aimed to protect personal data were enforced in order to protect privacy and to prevent the identification of individual data. In practice, each identification code was automatically converted to a unique and anonymous code, and the inverse process was prevented by the deletion of the conversion table.

Cohort selection and follow-up

All women aged 45–75 years who received at least one HRT prescription anytime during 1998–2000, were identified from the outpatient prescription drug database. These drugs included all those used in Italy to treat symptoms of menopause (oestrogens or estradiol alone or conjugated with progestin) and modes of administration (ovules, gels, patches and pills).

Each woman accumulated person-years of follow-up from the date of the first recorded prescription of a drug for HRT (index prescription) until the earliest of the dates of death, hospitalization for cancer, cardiovascular disease or fracture, emigration or December 31, 2005.

Eligible women who, in the period from January 1, 1997 to the date of the index prescription, took at least one prescription of HRT or were hospitalized for cancer or cardiovascular disease, and those who did not have at least 6 months of follow-up, were excluded.

Case and control selection

Case patients were all the members of the cohort hospitalized with main cause recorded as fracture (codes 800–829

according to the International Classification of Diseases, 9th Revision) during follow-up. Up to six controls for each case were selected randomly within the cohort after they were matched for age at cohort entry, date of cohort entry and were at risk for the outcome at the time of the matched case event (index date).

Cases and controls who during follow-up were hospitalized for malignancy, severe alcohol misuse, psychosis, or senile dementia were not considered for this study.

Use of HRT and concomitant conditions

The type and the dose of each HRT prescription dispensed to the cases and controls from cohort entry until the index date were retrieved from the outpatient prescription drug database. The conjugated-oestrogen dose equivalent was calculated for each dispensed prescription (0.625 mg of conjugated oestrogens were considered equivalent to 0.625 mg of esterified oestrogens and to 0.05 mg of ethinyl oestrogens [33]), and the resulting defined daily dose units, established as the typical adult's daily maintenance dose [34], was calculated for each prescribed drug. For overlapping prescriptions, the individual was assumed to have refilled early and completed the first prescription before starting the second. An indicator of the duration of HRT use during follow-up was constructed by summing up the number of days with medication available and categorized according to the following four approximately equal-sized categories measured in controls: ≤ 2 months, 2–6 months, 6–20 months and > 20 months.

How recently HRT had been used was calculated according to the time interval since last HRT use until the index date. It was categorized into mutually exclusive groups of current, recent, and past use. Current use was defined as HRT use in the period of 6 months before or at the index date, including ongoing treatment at the index date, recent use as exposure in the period of 6–12 months before the index date and past use as exposure in the period of 12 months or more before the index date.

Hospital discharges for thyroid disease (ICD-9: 240–246), diabetes (250), chronic renal failure (585) and connective tissue diseases (710), and prescriptions for corticosteroids for systemic use (H02) and for drugs used for diabetes (ATC code: A10), thyroid therapy (H03), and osteoporosis (e.g. biphosphonates: M05BA, M05BB; calcitonin: H05BA; and raloxifene: G03XC01), experienced by each case and control during follow-up were recorded. Hospital discharges for fracture which occurred from January 1, 1997 until the date of cohort entry were also recorded.

Data analysis

Univariate logistic regression was used to compare cases and controls according to each of the subject's characteristics measured at cohort entry or during follow-up.

Multivariate logistic regression was then used to estimate OR, and to calculate its 95% CI, for the association

between HRT and the risk of fracture. The independent effect of the categories of cumulative duration of HRT use and its combined effect with the categories of how recently HRT had been used (recency) were estimated, respectively, by including in the model only the main term of duration and also the main term of recency and the interaction term between duration and recency. Trend in ORs were tested, when feasible, according to the statistical significance of the regression coefficient of the recoded variables obtained by scoring the corresponding categories. Separate analyses according to three categories of age at cohort entry (45–55, 56–65, and 66–75 years) were carried out. All the models included the following terms: (i) signs suggestive of thyroid disease, diabetes, chronic renal failure, connective tissue diseases and osteoporosis, each categorized as sign present vs. no signs recorded during follow-up; (ii) duration of corticosteroid use during follow-up categorized as no use, use for less than 6 months, and use for 7 months or more; (iii) history of bone fractures which occurred prior to the date of cohort entry categorized as positive vs. negative history.

Due to the matching procedure, the parameters of both univariate and multivariate logistic models were estimated by maximizing the conditional likelihood function [35].

The corresponding calculations were carried out using the PHREG procedure of the SAS package [36]. For all hypotheses tested two-tailed *P* values less than 0.05 were considered to be significant.

Results

During 1998–2000, 87 568 women who received at least one prescription of a commonly prescribed HRT drug for the first time were identified. Nine thousand two hundred and seventy-four were excluded because they were hospitalized for cancer or cardiovascular disease during follow-up, or because they did not complete at least 6 months of follow-up. The remaining 78 294 women included in the cohort had accumulated 470 042 person-years of observation during which 2 473 465 prescriptions for HRT were dispensed and 1321 hospitalizations for fracture occurred, with a rate of about 28 cases per 10 000 person-years. Among the 1321 women who experienced at least one fracture during follow-up, 147 were excluded because of concomitant signs of malignancy, severe alcohol misuse, psychosis, or senile dementia. The remaining 1174 cases, whose mean age (SD) was 60.1 years (8.2) at the index date, were matched to 6760 controls who also met the inclusion criteria. Fracture sites of included cases were upper limb 374, lower limb 306, hip 221, spine 118, skull 57, and other sites 98.

Table 1 summarizes the selected characteristics of cases and controls. Compared with controls, case patients had bone fractures more frequently prior to the index prescription. During follow-up, cases experienced shorter use and earlier interruption of HRT than controls. However, cases were also more frequently affected by chronic renal

Table 1

Selected traits of the 1174 cases of fracture and 6760 controls included in the study. Lombardia Region, Italy, 1998–2005

	Case patients	Controls	<i>P</i> value†
History of fracture prior the index prescription	13 (1.1%)	34 (0.5%)	0.0076
Duration of exposure to HRT‡			
≤2 months	350 (29.8%)	1691 (25.0%)	<0.0001
2–6 months	360 (30.7%)	1751 (25.9%)	
6–20 months	260 (22.1%)	1628 (24.1%)	
>20 months	204 (17.4%)	1690 (25.0%)	
Time interval since HRT use§			
Current use	292 (24.9%)	2242 (33.2%)	<0.0001
Recent use	117 (10.0%)	607 (9.0%)	
Past use	765 (65.1%)	3911 (57.9%)	
Prevalence of selected diseases during follow-up			
Thyroid disease	27 (2.30%)	162 (2.40%)	0.8412
Diabetes	76 (6.47%)	348 (5.15%)	0.0623
Chronic renal failure	3 (0.26%)	2 (0.03%)	0.0044
Connective tissue disease	5 (0.43%)	10 (0.15%)	0.0430
Osteoporosis	39 (3.32%)	98 (1.45%)	0.0001
Users of corticosteroids during follow-up	93 (7.92%)	415 (6.14%)	0.0213

†According to chi-square statistics, or its version for the trend (duration and time interval since HRT use), based on univariate conditional logistic regression; ‡According to the time interval spent with available HRT during follow-up categorized into four approximately equal-sized categories measured in controls; §According to the time interval since last HRT use before the index date. Current use: less than 6 months, including ongoing treatment at the index date. Recent use: from 6–12 months before the index date. Past use: 12 months or more before the index date.

Table 2

Adjusted odds ratios, and corresponding 95% confidence intervals, of fracture risk associated with categories of duration of HRT use in all, current, recent, and past users. Lombardia Region, Italy, 1998–2005

		Duration of HRT use†			
		≤2 months	2–6 months	6–20 months	>20 months
All users	Cases/Controls	350/1691	360/1751	260/1628	204/1690
	OR	1.00	1.04	0.96	0.80*
	(95% CI)	(reference)	(0.88, 1.23)	(0.80, 1.15)	(0.65, 0.99)
	Trend test (P value)			0.0432	
Current users‡	Cases/Controls	17/66	46/282	113/768	116/1126
	OR	1.00	0.97	0.97	0.71*
	(95% CI)	(reference)	(0.66, 1.41)	(0.76, 1.25)	(0.55, 0.90)
	Trend test (P value)			0.0559	
Recent users‡	Cases/Controls	32/134	38/175	23/154	24/144
	OR	1.00	1.14	0.82	1.01
	(95% CI)	(reference)	(0.76, 1.70)	(0.51, 1.32)	(0.63, 1.61)
	Trend test (P value)			0.6087	
Past users‡	Cases/Controls	301/1491	276/1294	124/706	64/420
	OR	1.00	1.05	0.97	0.97
	(95% CI)	(reference)	(0.87, 1.26)	(0.76, 1.23)	(0.71, 1.34)
	Trend test (P value)			0.9329	

†According to the time interval spent with available HRT during follow-up categorized into four approximately equal-sized categories measured in controls; ‡According to the time interval since last HRT use before the index date. Current use: less than 6 months, including ongoing treatment at the index date. Recent use: from 6–12 months before the index date. Past use: 12 months or more before the index date *P < 0.05. Estimates are adjusted for signs suggestive of thyroid disease, diabetes, chronic renal failure, connective tissue disease, and osteoporosis recorded during follow-up, cumulative duration of corticosteroids use during follow-up, and history of bone fractures occurring prior to the index prescription.

failure, connective tissue diseases and osteoporosis and more often used corticosteroids.

The independent effect of duration of HRT use on the risk of fracture, and its combined action with how recently HRT had been used, are shown in Table 2. A significant trend toward decreasing ORs as duration of treatment increased was found in all women. Compared with women who used HRT for less than 2 months, those who were treated for more than 20 months had an OR of 0.80 (95% CI 0.65, 0.99). A significant effect was also observed for current users with an OR of 0.71 (95% CI 0.55, 0.90) for the longest duration of use. Conversely, there was no statistical evidence that duration affected the risk of fracture in women who had stopped treatment more than 6 months before the index date.

Table 3 shows the relationship between duration of HRT use and risk of fractures according to the age at the index prescription. There was no statistical evidence of risk reduction in younger women. Conversely, a significant trend towards decreasing ORs as duration of treatment increased was found in older women. Treatment for more than 20 months was associated with ORs of 0.63 (0.42, 0.94) and 0.56 (0.32, 0.99) for women aged 55–65 years and 65–75 years, respectively.

Discussion

Our study supports the evidence that HRT reduces the risk of fracture. The protective effect was observed for women

who used HRT for 20 months or more, particularly in the current user group. Our results also suggest that the fracture reducing potential of HRT seems limited to women who are older than 55 years at initiation of therapy.

Several observational studies [18, 21, 24, 30], randomized clinical trials [25, 28, 29, 31, 37, 38], and a number of meta-analyses [15, 26, 27], have consistently shown that HRT protects postmenopausal women against fractures. Moreover, different studies support our finding that the effect of HRT on fracture risk dissipates after stopping treatment [9, 16, 17, 21, 24, 32].

Evidence regarding the age at initiation of treatment is conflicting. No evidence that age might affect the fracture reducing potential of HRT was found in a meta-analysis of randomized trials [26]. Consistent with our findings, however, a recent case-control study has shown that the fracture reducing potential of HRT was greater in women aged 60 years or more, compared with those aged 50–59 years [30].

Our findings are apparently in disagreement with those reporting the fracture reducing potential of HRT among women who begin hormonal treatment in the early postmenopausal years [21]. In addition, HRT administration for 2–3 years in the early postmenopausal years has also been reported to prevent bone loss and osteoporotic fractures, even many years after stopping HRT [38]. However, these studies had a longer follow-up period. Therefore we cannot exclude the possibility that younger women who use HRT for long periods in the early postmenopausal years may have a reduced fracture risk many years afterwards.

Table 3

Adjusted odds ratios, and corresponding 95% confidence intervals, of fracture risk associated with categories of duration of HRT use according to age at the index prescription. Lombardia Region, Italy, 1998–2005

Age at the index prescription		Duration of HRT use†	2–6 months	6–20 months	>20 months
		≤2 months			
45–55 years	Cases/Controls	75/671	81/770	116/973	147/1269
	OR	1.00	0.95	1.06	0.97
	(95% CI)	(reference)	(0.68, 1.33)	(0.77, 1.45)	(0.71, 1.31)
	Trend test (P value)		0.9818		
56–65 years	Cases/Controls	125/643	138/639	85/495	39/342
	OR	1.00	1.12	0.88	0.63*
	(95% CI)	(reference)	(0.85, 1.46)	(0.65, 1.20)	(0.42, 0.94)
	Trend test (P value)		0.0270		
66–75 years	Cases/Controls	150/377	141/342	59/160	18/79
	OR	1.00	1.06	0.95	0.56*
	(95% CI)	(reference)	(0.80, 1.41)	(0.66, 1.36)	(0.32, 0.99)
	Trend test (P value)		0.0485		

†According to the time interval spent with available HRT during follow-up categorized into four approximately equal-sized categories measured in controls; *P < 0.05; Estimates are adjusted for signs suggestive of thyroid disease, diabetes, chronic renal failure, connective tissue disease, and osteoporosis recorded during follow-up, cumulative duration of corticosteroids use during follow-up, and history of bone fractures occurring prior to the index prescription.

The main strengths of our study are the uniformly organized health care system which allowed a large-scale population-based design, and the use of data on exposure and confounders that were collected before the date of fracture. Thus, recall bias did not affect data collection.

The weaknesses include potential selection bias, e.g. the use of routine hospital discharge diagnoses of fractures coded by hospital doctors to ascertain case status. Some coding errors have probably occurred. However, misclassification of case status is unlikely to be related to prescription of HRT before hospitalization, and any nondifferential misclassification is likely to lead to underestimation of our risk estimates.

We cannot exclude that information bias may have affected our results. We had no information on patient compliance, since redeeming a prescription was used as a proxy for actual use of a drug. Furthermore, data on drugs administered during hospitalization are not registered in the prescription database. Both these uncertainties could have led to misclassification of the exposure.

Because our study did not capture exposures which occurred prior 1997, overestimates of the protective effect of HRT could be expected, mainly in older women.

We took into account several potential confounding factors. Patients at higher risk of fractures (i.e. those affected by malignancy, severe alcohol misuse, psychosis, or senile dementia) were excluded. Furthermore, our estimates were adjusted for the effect of several conditions known to increase the risk of fractures (including thyroid disease, diabetes, chronic renal failure, connective tissue diseases and osteoporosis, use of corticosteroids, and history of bone fractures). In spite all these precautions, we cannot exclude that our results may still have been affected by confounding factors which were omitted, e.g.

smoking, physical activity, body mass index, and use of calcium/vitamin D supplements.

Our study compared very short-term with longer-term HRT users. This might have some advantages in reducing the effect of unmeasured confounding factors with respect to studies that compare users and never users, and perhaps might explain some of the contrasting findings.

A further issue, even in our comparatively large study, is the low statistical power in some subgroups, so limiting the interpretation of statistically nonsignificant ORs.

In conclusion our study suggests that in order to achieve the most effective protection against fracture, HRT should be continued for long periods, even though this may be considered unacceptable by many clinicians due to the postulated risks associated with breast cancer and cardiovascular disease. The fracture reducing potential of HRT seems to disappear after few months without treatment and is more effective in women who begin therapy at an older age.

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