Original Contribution

Risk of Osteoporotic Fractures After Discontinuation of Menopausal Hormone Therapy: Results From the E3N Cohort

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While current use of menopausal hormone therapy (MHT) reduces the risk of osteoporotic fractures, epidemiologic studies suggest that protection wears off rapidly after discontinuation of treatment. The authors identified 5,589 first osteoporotic fractures (2,235 major osteoporotic fractures) among 70,182 postmenopausal women from the French E3N cohort (1992–2008) and used Cox multivariate proportional hazards regression models to estimate hazard ratios. Persistence of protection against major osteoporotic fractures after MHT discontinuation was only observed when MHT had been used for at least 5 years, with a slightly more important decrease within the 5 years after discontinuation (compared with never use of MHT, hazard ratio = 0.68, 95% confidence interval: 0.50, 0.92) than beyond 5 years (hazard ratio = 0.83, 95% confidence interval: 0.69, 0.99); the P value for homogeneity between the 2 estimates was not significant. Oral estrogen use and transdermal estrogen use conveyed similar estimates in past users. Among current users, the authors confirmed a protective effect of MHT against risk of osteoporotic fractures. These findings, which relied on a number of MHT combinations, suggested that such therapies should be used for 5 years or more for reducing risk of fracture after treatment discontinuation.

cohort studies; estrogen replacement therapy; osteoporosis; osteoporotic fractures; postmenopause

Abbreviations: CI, confidence interval; E3N, Etude Épidémiologique de Femmes de la Mutuelle Générale de l’Education Nationale; HR, hazard ratio; MHT, menopausal hormonal therapy; MOF, major osteoporotic fracture; WHI, Women’s Health Initiative.

Osteoporotic fractures, especially of the hip, may be associated with severe disability, loss of independence, diminished quality of life, and reduced survival, and they constitute a substantial burden worldwide (1). In the United States, lifetime risk of hip, spine, or forearm fracture has been estimated at nearly 40% in white women over the age of 50 years (2). The risk of fractures increases with age, especially for women going through menopause; the main explanations are the decrease in bone mineral density due to the decrease of estrogen levels after menopause (3) and an increased risk of falls in the elderly (4).

Menopausal hormone therapy (MHT) has been shown to reduce the incidence of postmenopausal fractures in both randomized trials (5–9) and observational studies (10, 11). However, concern about cardiovascular safety, as demonstrated by the Women’s Health Initiative (WHI) randomized controlled trial (12), along with the WHI and Million Women Study reports of increased breast cancer risk among estrogen-progestogen MHT users (13, 14), resulted in recommendations concerning the use of MHT for prevention of osteoporosis and osteoporotic fracture. Rapid and substantial decreases in MHT use were observed in a number of countries, including France, after 2002 (15), and MHT is now recommended only for as short a time as possible. Thus, the question of persistence of protection against osteoporotic fracture offered by MHT following its discontinuation is particularly important. Although protection has been found to wear off rapidly after cessation of treatment (10, 16),
further investigations are needed, especially taking into account duration of use and treatment type. Indeed, while several studies examined a potential differential effect of oral and cutaneous estrogens (10, 17, 18) and different types of estrogen-progestogen combinations (10) on the risk of osteoporotic fracture in current users, to our knowledge, no cohort study has examined these questions in women who stopped MHT.

Thus, we used data from a French cohort study containing detailed and updated information on MHT use and incidence of fracture to investigate these issues.

MATERIALS AND METHODS

The E3N cohort

The Etude Épidémiologique de Femmes de la Mutuelle Générale de l’Éducation Nationale (E3N) Study is a prospective cohort study initiated in 1990 that includes 98,995 French women born between 1925 and 1950 who are insured by a health insurance plan that mainly covers teachers. Participants, who gave written informed consent, completed biennial self-administered questionnaires sent to them from 1990 to 2008 on medical history, menopausal status, and a variety of lifestyle characteristics. Usual diet was assessed through a validated 208-item diet history questionnaire sent out between June 1993 and June 1995 (19). The study was approved by the French National Commission for Data Protection and Privacy.

Data on fractures

The occurrence of fractures was self-reported on each follow-up questionnaire, starting from the third one (sent out in 1993). The date of the fracture was systematically requested, along with information on the site (third, fourth, fifth, and eighth questionnaires) and circumstances (third and eighth). Between 2005 and 2007, additional questionnaires were sent to postmenopausal women to collect any missing information.

Although confirmation of fractures through radiography, surgery, or practitioner reports was not possible, available data on reimbursed radiographic examinations have been provided by the medical insurance company since 2004 and showed very good agreement (concordance = 81.4%, kappa = 0.69; unpublished results) between self-reports and examinations performed during a 2-month interval after osteoporotic fracture occurrence. In addition, a validation study was conducted in a randomly selected sample of 200 women who reported having an osteoporotic fracture in 2007. A total of 117 women sent back radiographic or medical reports which were validated by a physician on our team. According to the reimbursement files, 87% of nonrespondents underwent a radiographic examination after their osteoporotic fracture, although they were unable to retrieve and send us any related documents.

Except for fractures of the ribs, fingers, and face, each low-energy fracture (i.e., those not occurring after an accident, after falling from a height, or caused by disease) (2, 20) which occurred after menopause was considered an osteoporotic fracture in our study. Women reporting multiple fractures were assigned to only 1 relevant site according to the following hierarchy: proximal femur first, then spine, shoulder, leg, foot, ankle, wrist, and arm (10).

We first conducted a series of analyses of all osteoporotic fractures and then conducted a second analysis of a pool of fractures of the wrist, spine, and proximal femur (3 sites found to be strongly associated with osteoporosis (2)), which we termed major osteoporotic fracture (MOF).

Assessment of MHT use

Information on lifetime use of hormonal treatments was recorded on the 1992 questionnaire, which thus formed the baseline of the current report. For each treatment episode, data on brand name, age at initiation, and duration of use, but not dose or number of days of use per month, were requested. Information on MHT use was updated in each of the subsequent questionnaires.

In some analyses, users of MHT were classified according to the route of estrogen administration or the type of associated progestogen (if any). Route of estrogen administration was defined as either oral, cutaneous (i.e., systemic gel or patch), or other (including vaginal, nasal, or intramuscular). Progestogens were categorized as progesterone, dydrogesterone, pregnane derivatives (medroxyprogesterone acetate, chloropregesterone acetate, cyproterone acetate, medrogestone), nonpregnan derivatives (dimegestone, nomegestrol acetate, promegestone), and norsteroid (also called 19-nortestosterone) derivatives (norethisterone acetate, lynestrenol, dienogest, drospirenone, levonorgestrel). Tibolone was assigned to a separate category.

Women were classified as current users if they had used MHT at any time during the 3-month period prior to the date of completion of the questionnaire.

Definition of menopause

Information on menopausal status was updated in each questionnaire. Women were considered postmenopausal if they had had 12 consecutive months without menstrual periods (unless due to hysterectomy), had undergone bilateral oophorectomy, had used MHT, or reported that they were postmenopausal. Age at menopause was defined as age at the last menstrual period (if the last menstrual period occurred before any MHT use and if amenorrhea was not due to hysterectomy), age at bilateral oophorectomy, or, in decreasing order of priority, self-reported age at menopause, age at start of MHT, or age at start of menopausal symptoms. Women whose age at menopause could not be determined were considered to have become menopausal at age 47 years if menopause was artificial and at age 51 years otherwise. These ages corresponded to median ages for artificial and natural menopause, respectively, in the cohort (21).

Population for analysis

Follow-up began either on the date of return of the baseline questionnaire, for women who were already
postmenopausal, or on the date of the first report of meno-
pause. Participants contributed person-years of follow-up
until the first date of an osteoporotic fracture, the date of
the last completed questionnaire, the date of diagnosis of
any type of cancer, or July 2008 (the end of the study period,
which corresponds to the date on which the ninth question-
naire was sent to participants), whichever occurred first.

Among the 98,995 women in the E3N cohort, we ex-
cluded women who had not reported being postmenopausal
at the time of the eighth questionnaire (n = 10,728). We then
excluded the following: women who reported having an
osteoporotic fracture before the start of follow-up (n = 3,280);
women for whom the reported fracture could not be classified
as osteoporotic or nonosteoporotic (n = 2,775; for 466 women,
no information could be retrieved because of death, an invalid
address, dropout, or nonre-
sponse; the remaining 2,309 women gave incomplete infor-
mation), women who had been diagnosed with cancer (other
than basal cell carcinoma) before the start of follow-up (n = 6,627);
women with no follow-up (n = 2,804); and women who did not answer the baseline questionnaire about life-
time MHT use and were already postmenopausal on the date
on which this questionnaire was sent (n = 2,599). This left
us with 70,182 women for analysis.

Table 1. Selected Characteristics of Participants According to Ever Use of Menopausal Hormone Therapy at the End of Follow-up (n = 70,182),
E3N Cohort, 1992–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never Users of MHT (n = 18,651)</th>
<th>Ever Users of MHT (n = 51,531)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Year of birth</td>
<td>1925–1929</td>
<td>2,730</td>
</tr>
<tr>
<td></td>
<td>1930–1934</td>
<td>3,368</td>
</tr>
<tr>
<td></td>
<td>1935–1939</td>
<td>3,197</td>
</tr>
<tr>
<td></td>
<td>1940–1944</td>
<td>3,470</td>
</tr>
<tr>
<td></td>
<td>1945–1949</td>
<td>5,886</td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;20</td>
<td>2,122</td>
</tr>
<tr>
<td></td>
<td>20–25</td>
<td>10,321</td>
</tr>
<tr>
<td></td>
<td>&gt;25</td>
<td>6,208</td>
</tr>
<tr>
<td>Educational level</td>
<td>High school graduate</td>
<td>3,800</td>
</tr>
<tr>
<td></td>
<td>College graduate</td>
<td>12,124</td>
</tr>
<tr>
<td></td>
<td>Postgraduate study</td>
<td>2,727</td>
</tr>
<tr>
<td>Total physical activity in 1990, MET-hours/week</td>
<td>&lt;27</td>
<td>4,223</td>
</tr>
<tr>
<td></td>
<td>27–38</td>
<td>4,324</td>
</tr>
<tr>
<td></td>
<td>39–51</td>
<td>4,070</td>
</tr>
<tr>
<td></td>
<td>≥52</td>
<td>6,034</td>
</tr>
<tr>
<td>Ever use of calcium supplements</td>
<td>No</td>
<td>17,498</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1,153</td>
</tr>
<tr>
<td>Calcium intake, mg/day</td>
<td>1,042.8 (415.9)</td>
<td>1,048.8 (403.0)</td>
</tr>
<tr>
<td>Alcohol intake, g of ethanol/day</td>
<td>10.3 (14.2)</td>
<td>11.4 (14.1)</td>
</tr>
</tbody>
</table>

Table continues

Statistical analysis

Known risk factors for fracture and potential confounders
(improving the model fit by the P < 0.05 criterion) were
included in the final models, which were therefore adjusted
for all of the parameters indicated in the table footnotes.
We also considered other parameters which were not re-
tained in the final model because they did not improve the
model fit and were not altering the hazard ratio: smoking
status (current smoker, ex-smoker, or never smoker; time-
dependent variable), maternal history of hip fracture (yes/
no; data were collected on the third questionnaire), personal
history of premenopausal fracture (yes/no), personal history
of postmenopausal nonosteoporotic fracture (occurring after
high trauma, disease, or fractures of the ribs, fingers, or
face) (yes/no; time-dependent variable), personal history
of hypertension, venous thromboembolism, myocardial
infarction, stroke, diabetes, asthma, or thyroid disease
(time-dependent variables), and daily intakes (in grams) of
calcium (22) and alcohol as assessed from the dietary
questionnaire.

Models were further stratified on year of birth, using
5-year categories to take into account birth cohort effects
(23). Imputation to the median (for continuous variables) or
mode (for discrete variables) was used in cases of missing values (5% or less for each of them).

For MHT exposure status, as well as for time-dependent covariates, data recorded on questionnaires $i$ and earlier were used to prospectively categorize women for the period that followed (i.e., between questionnaire $i$ and questionnaire $j$, where $j$ was the next questionnaire completed). The reference group in each model consisted of women who indicated that they had never used any MHT.

Tests for trends in duration of use were conducted in models that included duration of use as a continuous variable. Model parameters were estimated and compared using likelihood methods and Wald tests. All analyses were performed with SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

A total of 5,589 first osteoporotic fractures occurred among the 70,182 women included in the analysis during 808,525 person-years of follow-up (mean duration = 11.5 years (standard deviation, 4.4)). Of these first osteoporotic fractures, 2,235 were MOFs (among them, 78.8% occurred at the wrist, 8.0% at the proximal femur, and 13.2% at the spine). The average age at the start of follow-up was 53.8 years (standard deviation, 4.5). Characteristics of the study population according to ever use of MHT are presented in Table 1.

Compared with never use of MHT, we observed a significant decrease in the risks of osteoporotic fracture and MOF associated with ever use of MHT (Table 2). Current users had significant 22% and 30% reductions in the risks of osteoporotic fracture (hazard ratio (HR) = 0.78, 95% confidence interval (CI): 0.73, 0.83) and MOF (HR = 0.70, 95% CI: 0.63, 0.77), respectively, in comparison with never users, while overall, past users of MHT had no significantly decreased risk of fracture (HR = 0.99 (95% CI: 0.92, 1.06) and HR = 0.93 (95% CI: 0.83, 1.04) for osteoporotic fracture and MOF, respectively). The decrease in risk persisted with borderline significance for osteoporotic fracture and MOF during the 5 years after MHT arrest (HR = 0.92
HR = 0.85 (95% CI: 0.73, 0.99), respectively) but not thereafter (HR = 1.05 (95% CI: 0.96, 1.14) and HR = 0.98 (95% CI: 0.86, 1.12), respectively) (Table 2).

We also found significant trends toward decreasing risks of osteoporotic fracture and MOF with increasing duration of MHT use among women who had stopped using MHT at least 5 years previously (Table 2). As a consequence, women who had stopped using MHT 5 or more years previously but had used MHT for at least 5 years were still at significantly decreased risk of MOF in comparison with never users of MHT (HR = 0.83, 95% CI: 0.69, 0.99), although the risk reduction was less marked than that seen among women who had used MHT for at least 5 years and had stopped using it within the past 5 years (HR = 0.68, 95% CI: 0.50, 0.92) or were still current users (HR = 0.65, 95% CI: 0.57, 0.74). In current users and women who had stopped using MHT less than 5 years previously, there were also apparent trends toward decreasing risk with increasing duration; however, this reached statistical significance only for the risk of MOF associated with current MHT use ($P$ for trend = 0.05).

Table 3 shows the risks of fracture according to the route of administration of the estrogen component of MHT and recency of use. There was no significant difference between hazard ratios associated with past use of oral MHT and past

| Table 2. Hazard Ratio for Osteoporotic Fracture Associated With Ever Use of Menopausal Hormone Therapy as Compared With Never Use ($n = 70,182$), E3N Cohort, 1992–2008 |
|---------------------------------|-----------------|-----------------|
| Osteoporotic Fractures ($n = 5,589$) | Major Osteoporotic Fractures ($n = 2,235$) |
| No. of Cases $^a$ | HR $^b$ | 95% CI | No. of Cases $^a$ | HR $^b$ | 95% CI |
| Never use of MHT | 1,981 | 1 | Reference | 835 | 1 | Reference |
| Ever use of MHT | 3,608 | 0.85 | 0.81, 0.91 | 1,400 | 0.79 | 0.72, 0.86 |
| Current use of MHT | 2,083 | 0.78 | 0.73, 0.83 | 774 | 0.70 | 0.63, 0.77 |
| Past use of MHT | 1,480 | 0.99 | 0.92, 1.06 | 608 | 0.93 | 0.83, 1.04 |
| Stopped using MHT $<5$ years previously | 554 | 0.92 | 0.83, 1.01 | 213 | 0.85 | 0.73, 0.99 |
| Stopped using MHT $\geq 5$ years previously | 872 | 1.05 | 0.96, 1.14 | 368 | 0.98 | 0.86, 1.12 |

$^a$ Recency of use (current/past) was unknown for 45 cases of osteoporotic fracture (18 major osteoporotic fractures); duration of use was unknown for 269 cases of osteoporotic fracture (114 major osteoporotic fractures); and time since discontinuation was unknown for 54 cases of osteoporotic fracture (27 major osteoporotic fractures).

$^b$ Adjusted for body mass index (weight (kg)/height (m)$^2$ ($<20$, $20–25$, or $>25$); time-dependent), physical activity in 1990 (in metabolic equivalent-hours/week ($<27$, $27–38$, $39–51$, or $>52$)), age at menopause ($<47$, $47–54$, or $>54$ years), parity (number of full-term pregnancies), previous use of oral contraceptives (ever/never), previous use of calcium supplements (yes/no; time-dependent), and educational level (high school graduate, college graduate, or postgraduate study).

**Table 3.** Hazard Ratio for Osteoporotic Fracture Among Ever Users of Menopausal Hormone Therapy (in Comparison With Never Use) According to the Route of Estrogen Administration and Recency of Use (n = 70,182), E3N Cohort, 1992–2008

<table>
<thead>
<tr>
<th></th>
<th>Oral Estrogens*</th>
<th>Cutaneous Estrogens*</th>
<th>P for Homogeneity</th>
<th>P for Homogeneity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Casesb</td>
<td>HRc</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>All osteoporotic fractures (n = 5,589)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>427</td>
<td>0.69</td>
<td>0.63, 0.77</td>
<td></td>
</tr>
<tr>
<td>Treatment stopped &lt;5 years previously</td>
<td>291</td>
<td>0.99</td>
<td>0.88, 1.12</td>
<td></td>
</tr>
<tr>
<td>Treatment stopped ≥5 years previously</td>
<td>368</td>
<td>1.00</td>
<td>0.89, 1.11</td>
<td></td>
</tr>
<tr>
<td>Major osteoporotic fractures (n = 2,285)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>154</td>
<td>0.63</td>
<td>0.53, 0.74</td>
<td></td>
</tr>
<tr>
<td>Treatment stopped &lt;5 years previously</td>
<td>151</td>
<td>0.87</td>
<td>0.71, 1.07</td>
<td></td>
</tr>
<tr>
<td>Treatment stopped ≥5 years previously</td>
<td>482</td>
<td>0.98</td>
<td>0.83, 1.17</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l’Education Nationale; HR, hazard ratio; MHT, menopausal hormone therapy.

* Alone or combined with a progestogen.

b The sum of the numbers of cases exceeds the total number of cases among MHT ever users, since categories are not mutually exclusive; for example, a woman could contribute simultaneously to the “Oral estrogens, current use” and “Cutaneous estrogens, treatment stopped <5 years previously” categories if she had first used MHT containing cutaneous estrogens, had stopped the treatment 1 year previously, and currently used MHT containing oral estrogens.

c Adjusted for the same covariates as in Table 2.

d P value obtained after further adjustment for total duration of MHT use (<2, 2–4.9, or ≥5 years, or missing data).

Use of cutaneous MHT for either osteoporotic fracture or MOF, even when further adjustment was made for total duration of MHT use. In current MHT users, however, there was a significant difference in hazard ratios for osteoporotic fracture, with hazard ratios equaling 0.69 (95% CI: 0.63, 0.77) and 0.78 (95% CI: 0.72, 0.83) for oral and cutaneous MHT, respectively (P for homogeneity = 0.05).

Table 4 shows hazard ratios according to the type of MHT and recency of use. In current users, significant decreases in the risks of both osteoporotic fracture and MOF were found regardless of the type of MHT used (with the exception of tibolone), in comparison with MHT never users. No significant heterogeneity in risk estimates, even after adjustment for total duration of MHT use, was found (Table 4). In past users, no significant decrease in risk was seen regardless of the type of MHT, except for the combination of estrogens with dydrogesterone, which was associated with a significant decrease in MOF risk (for women who had discontinued MHT less than 5 years previously, HR = 0.79, 95% CI: 0.63, 0.99; for women who had discontinued MHT 5 or more years previously, HR = 0.74, 95% CI: 0.59, 0.92). However, hazard ratios associated with past use of the various types of MHT did not differ significantly, even after adjustment for total duration of MHT use (Table 4).

**DISCUSSION**

Although results from this large prospective study showed that overall, past users of MHT were no longer at decreased risk of fracture, the long follow-up period and the large number of events enabled us to conduct an accurate analysis of the remnant effect after cessation of MHT and indicated that the protective effect of MHT against MOF may persist even beyond 5 years after MHT discontinuation, provided that MHT was used for at least 5 years. Our results also add to the evidence that current use of different types of MHT combinations significantly decreases the incidence of osteoporotic fracture. While no significant difference was found in the risks associated with the various types of progestogen molecules in estrogen-progestogen MHT, investigation of route of administration showed that current use of oral estrogens was associated with a slightly stronger decrease in osteoporotic fracture risk than current use of transdermal estrogens.

Mechanisms by which MHT may decrease the risk of fractures include the inhibiting effects of estrogen on bone resorption. Estrogens reduce the production of bone-resorbing osteoclasts while promoting activation of bone-forming osteoblasts. Estrogen deficiency would thus lead to a rapid rise in osteoclast formation and activity, resulting in accelerated bone resorption (24). With regard to the effects of progestin on bone, previous experimental data suggested that progestin may be involved in regulation of bone turnover and might promote bone formation (25, 26); indeed, there is evidence that progestins may act directly on osteoblasts through a progesterone receptor (27).

A loss of the protective effect of MHT against risk of fractures after stopping treatment has been found in some (10, 16, 28) but not all (17, 29, 30) studies. Our results showed that protection against risk of MOF may remain effective after MHT withdrawal (although less markedly than when recently used) provided that the total duration of use exceeded 5 years. Although investigators in the Million Women Study (10) found no reduction in osteoporotic fracture risk among past MHT users, their risk estimates across different periods of treatment discontinuation were compatible with our results not taking into account total...
duration of use; however, those authors did not investigate the relation between long duration of MHT and risk of MOF across different periods of treatment discontinuation. In the WHI estrogen-progestogen randomized trial, the protective effect of conjugated equine estrogens plus medroxyprogesterone on the risk of fracture (after an average of 5.6 years of follow-up) decreased immediately after the intervention (16). Nevertheless, the lack of a significant difference between fracture risk estimates during and after the intervention \((P = 0.20)\), combined with the small number of events, did not enable the investigators to exclude a possible beneficial effect of MHT on MOF incidence after treatment discontinuation.

Like investigators in previous randomized clinical trials (6, 8, 9) and observational studies (10, 11, 18, 31), we found that significant protection against the risk of osteoporotic fracture is conferred by current use of MHT, notably for MOF, thus preventing hip, wrist, and vertebral fractures in the WHI randomized trial (6, 8). Additional evidence has been provided by studies showing an increase in bone mineral density among current MHT users (11), while the rate of bone loss returned to normal postmenopausal rates after cessation of treatment (32, 33).

Overall, oral and cutaneous estrogens had comparable protective effects on the risk of fracture, as observed in previous studies (10, 17, 18). Our results suggested a slightly more pronounced benefit of oral rather than transdermal MHT combinations. However, we cannot rule out the possibility that chance, or different estrogens doses according to route of administration, could partially explain our results, since the difference was restricted to current users.

### Table 4. Hazard Ratio for Osteoporotic Fracture Among Ever Users of Menopausal Hormone Therapy (in Comparison With Never Use) According to Type of Menopausal Hormone Therapy and Recency of Use \((n = 70,182)\), E3N Cohort, 1992–2008

<table>
<thead>
<tr>
<th>Current Use of MHT</th>
<th>Stopped Using MHT &lt;5 Years Previously</th>
<th>Stopped Using MHT ≥5 Years Previously</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>All osteoporotic fractures ((n = 5,589))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unopposed estrogens</td>
<td>224</td>
<td>0.71</td>
</tr>
<tr>
<td>Estrogens combined with progesterone</td>
<td>521</td>
<td>0.81</td>
</tr>
<tr>
<td>Estrogens combined with dydrogesterone</td>
<td>302</td>
<td>0.74</td>
</tr>
<tr>
<td>Estrogens combined with pregnane derivatives</td>
<td>326</td>
<td>0.76</td>
</tr>
<tr>
<td>Estrogens combined with norpregnane derivatives</td>
<td>385</td>
<td>0.79</td>
</tr>
<tr>
<td>Estrogens combined with norsteroid derivatives</td>
<td>93</td>
<td>0.64</td>
</tr>
<tr>
<td>Tibolone</td>
<td>58</td>
<td>0.89</td>
</tr>
<tr>
<td>Unknown/other (c)</td>
<td>174</td>
<td>0.98</td>
</tr>
<tr>
<td>(P) for homogeneity (d)</td>
<td>0.23</td>
<td>0.22</td>
</tr>
<tr>
<td>(P) for homogeneity (e)</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td>Major osteoporotic fractures ((n = 2,285))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unopposed estrogens</td>
<td>74</td>
<td>0.59</td>
</tr>
<tr>
<td>Estrogens combined with progesterone</td>
<td>178</td>
<td>0.68</td>
</tr>
<tr>
<td>Estrogens combined with dydrogesterone</td>
<td>121</td>
<td>0.73</td>
</tr>
<tr>
<td>Estrogens combined with pregnane derivatives</td>
<td>132</td>
<td>0.77</td>
</tr>
<tr>
<td>Estrogens combined with norpregnane derivatives</td>
<td>136</td>
<td>0.69</td>
</tr>
<tr>
<td>Estrogens combined with norsteroid derivatives</td>
<td>29</td>
<td>0.50</td>
</tr>
<tr>
<td>Tibolone</td>
<td>26</td>
<td>1.03</td>
</tr>
<tr>
<td>Unknown/other (c)</td>
<td>78</td>
<td>1.02</td>
</tr>
<tr>
<td>(P) for homogeneity (d)</td>
<td>0.26</td>
<td>0.34</td>
</tr>
<tr>
<td>(P) for homogeneity (e)</td>
<td>0.23</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E3N, Etude épidémiologique des femmes de la Mutuelle Générale de l’Education Nationale; HR, hazard ratio; MHT, menopausal hormone therapy.

\(a\) The sum of the numbers of cases exceeds the total number of cases among MHT ever users, since categories are not mutually exclusive; for example, a women could contribute simultaneously to the “Estrogens combined with progesterone, current use” and “Tibolone, treatment stopped <5 years previously” categories if she had first used tibolone, had stopped the treatment 1 year previously, and currently used a combination of estrogen and progesterone.

\(b\) Adjusted for the same covariates as in Table 2.

\(c\) MHT containing promestriene, estriol, or androgen; MHT that was vaginally, nasally, or intramuscularly administered; MHT with transdermally administered progestogen; or MHT with no specified formulation.

\(d\) Excludes the “unknown/other” category.

\(e\) \(P\) value obtained after further adjustment for total duration of MHT use (<2, 2–4.9, or ≥5 years, or missing data).
Investigations of the relation between types of estrogen combinations and risk of osteoporotic fracture are scarce (10, 29, 34) and have been mainly restricted to current users (10, 34). Consistent with previously published studies and WHI trials (6, 8), we found no difference between the types of MHT. Possibly because of the short duration of MHT use (2.6 years, on average) and the relatively small number of osteoporotic fracture cases (n = 84) in this category, we did not find that tibolone significantly decreased the risk of fractures as previously described (35). The WHI trial found that fracture risk reduction did not persist after MHT discontinuation for the estrogen-plus-medroxyprogesterone acetate combination (16). Although the Million Women Study investigators explored the effect of estrogen treatment alone, norethisterone acetate, or levonorgestrel (10) on the risk of osteoporotic fracture in current MHT users, they did not examine other estrogen combinations after therapy cessation. Our results following MHT withdrawal showed ambiguous benefits with MHT combinations. In particular, significant residual protection against MOF with past use of an estrogen-plus-dydrogesterone combination, though possibly due to chance, highlights the importance of carrying out further investigations into the effects of different types of MHT after cessation of use.

Our study had several important strengths. Data on MHT exposure were updated every 2 years and were prospectively analyzed, thus eliminating the possibility of differential recall between cases and noncases. Good agreement had been previously observed between prescription data and self-reported use of MHT (36) and between self-reported MHT use on the eighth questionnaire and data from reimbursement files concurrently provided by the medical insurance company (concordance = 89.3%, kappa = 0.74). Our population, mainly composed of teachers, was quite homogeneous in terms of socioeconomic status, a potentially confounding factor. All analyses were adjusted for known risk factors for osteoporotic fracture, and validation studies of other endpoints demonstrated that the answers provided by our participants were very reliable (21).

Among important limitations of our study, not all osteoporotic fractures could be verified through radiographic or surgery reports. Very good agreement was found between self-reports of fracture and data from reimbursed examination files provided by the medical insurance company, as well as fractures reported in the validation study. Nevertheless, it is likely that some osteoporotic fractures, such as asymptomatic vertebral fractures, were not included in the present analysis. Underreporting of osteoporotic fractures is generally uncommon in the literature (37) and even less so in highly educated populations (38), as is the case with women in the E3N cohort: The WHI investigators previously demonstrated the accuracy of self-reports of fracture (except for vertebral fractures), especially for MOF (39). Nevertheless, the prevalence of vertebral fractures in our study (13.2%) was very close to that of an earlier European study (40).

We did not record details on MHT use and hence could not analyze risk associated with intermittent or continuous use or with dose or indication (climacteric symptoms, osteopenia). However, in the Million Women Study, fracture risk reductions for doses higher and lower than 0.625 mg of conjugated equine estrogens were similar, and no differences were observed for sequential or continuous preparations (10). Decreased risk of fracture did not differ according to bone mineral density before treatment in the WHI (6), thus limiting any indication bias.

Lastly, we decided to remove from the analysis women who had prevalent osteoporotic fractures at the start of follow-up, to avoid confounding in the estimations—first because women with a previous history of osteoporotic fracture have an increased risk of subsequent fractures (41) and second because thereafter they could have started other osteoporosis therapies. Indeed, although we did not have reliable information on corticotherapy or osteoporosis treatments and thus could not exclude from the analysis women using such treatments, given the mean age of the cohort at baseline (54 years) and the fact that these therapies are mainly prescribed after the first occurrence of osteoporotic fracture, the proportion of women who had been using effective osteoporosis treatments (such as bisphosphonates) was probably small.

In conclusion, although our findings are in close agreement with previous studies showing a benefit of current MHT use in the risk of osteoporotic fractures, they suggest that a remnant effect of such therapy might occur after long-term use. Because of safety concerns regarding breast cancer and cardiovascular diseases, it is currently recommended that MHT be used for the shortest possible duration of time. Our results suggest that such a short duration, whatever the progestogen molecule or route of administration, cannot reduce the risk of fracture over the medium or long term.

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Conflict of interest: none declared.

REFERENCES


