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Maturitas 11/2005; 52(3-4): 296-305

# Estimated numbers of postmenopausal women treated by hormone therapy in France

**Angèle Gayet-Ageron[a], Nassira Amamra[a], Virginie Ringa[h], Valérie Tainturier[b], Claudine Berr[c], Françoise Clavel-Chapelon[d], Cécile Delcourt[e], Pierre D. Delmas[f], Pierre Ducimetière[g], Anne-Marie Schott[a,*]**

*a Département d'Information Médicale des Hospices Civils de Lyon, 162 avenue Lacassagne, 69003 Lyon, France*
*b Direction régionale du service médical de l'Assurance Maladie, 26 rue d'Aubigny, 69003 Lyon, France*
*c INSERM E 361, 39 avenue Charles Flahault, 34093 Montpellier Cedex, France*
*d Institut Gustave Roussy, INSERM XU 521, 94805 Villejuif Cedex, France*
*e INSERM U 593, 148 rue Léo Saignat, 33076 Bordeaux Cedex, France*
*f Hôpital Edouard Herriot, INSERM U 403, pavillon F, 69003 Lyon Cedex, France*
*g Hôpital Paul Brousse, INSERM U 258, 94807 Villejuif Cedex, France*
*h INSERM U 149, Unité de recherches épidémiologiques en santé périnatale et santé des femmes, 16, avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France*

**Abstract**

*Objectives:* To estimate the number of women aged 50–69 years treated by hormone therapy (HT) in France before Women's Health Initiative's (WHI) results and to evaluate the potential decrease of HT prescriptions since the publication of WHI clinical trial.

*Methods:* We used data from eight computerized databases of French cohort studies providing information on HT and constituted by women aged over 50 years living in metropolitan France. From these, we used direct standardization on the French population to estimate the prevalence of HT users across 5 years age groups. Data from the National Health Insurance Agency on two timeperiods November 2002–January 2003 and November 2003–January 2004 were used to evaluate the evolution of HT prescriptions since WHI's publication among women aged 50–69 years living in the Rhône-Alpes region.

*Results:* The crude prevalence of HT users among women aged 50–69 years was 52.3% (51.8–52.8) and corresponds to a standardized prevalence of 35.7% (35.1–36.4), that is about 2.56 (2.51–2.59) million women. Standardized prevalence was the highest in 50–54 years age group then it decreased significantly across the older age groups ($p<10^{-6}$). HT reimbursements decreased significantly between the two studied time-periods in the Rhône-Alpes region ($p<10^{-6}$) from−14 to−45%, depending on the considered age groups (65–69 or 50–54 years).

*Conclusions:* Although WHI results have been criticized by French professional societies based on the fact that treatments used were different in France – mainly transdermal estrogens – and that French postmenopausal women were at lower vascular risk than those of the WHI, the release of this study had effect on the prescription before the French regulatory agency (AFSSAPS) edited limiting recommendations for HT prescription. Further efforts have to be made to collect systematically information on preventive treatments used at menopause followed by evaluation studies.

*Keywords:* Hormone replacement therapy; Prevalence; Prescriptions; Drug; Cohort studies; Practice guidelines; Postmenopause

## Introduction

Hormone therapy (HT) was for a long time considered as the miraculous pill, relieving menopausal symptoms and preventing the risk linked with the decrease in estrogens. However it has always produced heated discussions worldwide on both harmful and beneficial effects. Since the diffusion of the Women's Health Initiative's trial (WHI) results in July 2002 [1], completed 1 year later, by those of the Million Women Study (MWS) [2], clinical practices guidelines on HT use have been modified in most countries [3–5]. WHI, a clinical

* Corresponding author. Tel.: +33 4 72 11 51 65; fax: +33 4 72 11 57 20.
*E-mail address:* anne-marie.schott-pethelaz@chu-lyon.fr (A.-M. Schott).

trial conducted in 40 centers in the United States between 1993 and 1998, randomly assigned 16,608 healthy postmenopausal women aged 50–79 years, with an intact uterus, to combined conjugated equine estrogens plus progestogen or placebo. A third group of 10,739 hysterectomized women received estrogens alone. After a mean follow-up of 5.2 years, WHI showed increased estimated rates for coronary heart disease (hazard ratio [HR] 1.29; 95% confidence interval [CI95%]: 1.02–1.63), for invasive breast cancer (HR 1.26; CI95%: 1.00–1.59), for stroke (HR 1.41; CI95%: 1.07–1.85) and for pulmonary embolism (HR 2.13; CI95%: 1.39–3.25). On the contrary, hip fractures were proved to be reduced (HR 0.66; CI95%: 0.45–0.98), as well as colorectal cancer (HR 0.63; CI95%: 0.43–0.92). The risk-benefit profile was judged insufficiently positive to continue the clinical trial and it was stopped in July 2002. The MWS was an observational cohort of women aged 50–64 years, recruited between 1996 and 2001, through the National Health Service Breast Screening Program in United Kingdom. In this study, current use of HT was significantly associated with an increased risk of incident and fatal breast cancer, especially with estrogen–progestogen combinations (HR 2.00; CI95%: 1.88–2.12), whatever the formulations (oral, transdermal and implemented), and the risk increased with treatment duration. Following these results, the French Agency for Accreditation and Evaluation in Healthcare (ANAES) proposed revised clinical practices guidelines in May 2004 for the prescription of HT to postmenopausal women [3], which is now only recommended to healthy women who present climacteric symptoms that adversely affect their quality of life or in a second intention to prevent osteoporosis complications in women with high risk factors [3,6]. HT is recommended to be prescribed at a minimum effective dose and during a short time, which should be reevaluated every year.

The use of HT varies widely according to geographical area, from 2.5% among women aged 45–64 years in Japan [7] to 50% of women aged 50–65 years in North America [8]. To our knowledge, few estimations of HT use among French postmenopausal women had been performed and most of them used data from sampled French volunteers (SOFRES public opinion poll) or observational studies in selected groups of population [9–11].

*This study has two objectives*: firstly to estimate the number of postmenopausal women, aged between 50 and 69 years, treated by HT in France, based on eight French epidemiological cohorts, prior to WHI's results publication; secondly, to evaluate whether, although WHI and MWS were hardly criticized by French medical professional societies due to the fact that treatments used and study population were different, HT consumption decreased in France as in United States or in United Kingdom.

## Methods

This paper presents an analysis of data collected in a previous study estimating the prevalence of postmenopausal women with risk factors for osteoporosis in France [12]. This part of the study intends to estimate the prevalence of postmenopausal women treated with HT in France.

### *Study population*

We identified computerized databases of French cohort studies constituted by women aged over 50 years living in metropolitan France [13–20]. We have contacted the following institutions: the National Institute for Health Statistics and Research (Institut National de la Santé et de la Recherche Médicale, INSERM, website <http://www.inserm.fr>), the National Institute for Statistics and Economic Studies (Institut National des Statistiques et des Etudes Economiques, INSEE, 1990 census), and the National Electricity Company (Electricité de France, EDF). The list of the cohort studies is presented in Appendix A. Five studies were excluded due to the existence of major selection biases likely to affect the validity of our estimates, or due to population younger than 50 years, absence of validated information on HT use or due to non-representative populations. For example, the GAPIC study on coronary heart disease and other cardiovascular disorders was constituted mainly by men and does not answer to the objective; the "Health effects of exposure to water side products" study conducted among miners and swimmers could produce biases due to the selective population; in the study "benign breast disease and breast cancer risk", the mean age of women was too young to be relevant in our study; finally PAQUID study does not provide information on HT.

We also collected data from Rhône-Alpes regional database of the National Health Insurance Agency, which represents approximately 74% of women aged 50–69 years in this region (cf. INSEE census). The Rhône-Alpes region is one of the largest in France with an area of 43,500 km² and 5.5 million inhabitants. It has ~100 public hospitals, three university-teaching hospitals and 87 private hospitals, with a total of nearly 26,000 beds.

*Data collected*

To evaluate the prevalence of HT use among postmenopausal women and to measure the heterogeneity of the data used for our estimates, we asked the main investigators of the cohort studies to supply us with the exact wording of the items related to HT in their study questionnaires. All eight cohort studies collected information on current HT use at baseline, before WHI's results. One of them indicated that women were considered as current HT users (GAZEL). Another detailed the answers as "current user", "past user" with the time of beginning and end of HT and "never user" (ESTEV95). There was no information on the medical motive for HT prescription. Menopausal status was proved in E3N and GAZEL studies but in other cohorts, its determination was only based on age.

To evaluate the evolution of HT prescription since the publication of WHI's results, the National Health Insurance Agency for the Rhône-Alpes region provided the numbers of women aged between 50 and 69 years, who had obtained reimbursement for at least one prescription of HT (estrogen plus progestogen or estrogens alone) between November 2002–January 2003 (few months after the diffusion of WHI's results) and November 2003–January 2004 (more than 1 year after the diffusion of WHI's results). Data are regularly erased from the database where only information collected within the last 20 months are recorded. When we started the study, only data from November 2002 were available.We chose not to analyze a complete year from November 2002 to November 2003, since our objective was to compare the situation before and after the diffusion of WHI's results.We did not use these numbers to estimate the prevalence because the numerator concerned a 3-month period whereas the denominator was obtained in July 2004 so the prevalence would have been underestimated mainly due to women delaying their treatment issue. Absolute number of reimbursements provided between the two periods were compared for evaluating the evolution of HT prescriptions.

*Statistical analysis*

We first analyzed responses study-by-study on women aged over 50 years, then we pooled data from the eight cohorts to obtain estimates of HT prevalence among women aged between 50 and 69 years. Because the age distribution of our study sample differed from that of the overall population of postmenopausal women in France, we used direct standardization method on the National French population (1999 INSEE census) to correct our results [21]. Chi-square test for trend was used to evaluate the distribution of mean prevalence across the different age groups.

We then estimated the evolution of HT reimbursements in the Rhône-Alpes population from the National Health Insurance Agency database and we used Chisquare test for trend to compare absolute numbers of HT prescriptions between both periods, across the different age groups. To study the relative variation in HT reimbursement, we calculated the difference of absolute numbers between November 2002–January 2003 and November 2003–January 2004 related to the absolute number of HT reimbursement in November 2002–January 2003, for each age group.

*P*-values under 0.05 were considered significant. The analyses were carried out using EPI INFO 6.0 (Centers for Disease Control and Prevention, USA).

## Results

*Prevalence of HT use among the cohort studies*

Eight cohort studies were selected by our research procedure and provided information on HT use. The characteristics of women from each cohort are presented in Table 1. The eight studies represented a total of 119,629 women aged 50 years and over.

The prevalence of HT among women aged over 50 years is shown in Table 2. The overall average prevalence of HT use varied widely across the eight cohort studies, from 5.7% in the POLA cohort to 58.5% in the ESTEV95 cohort, for the reason that age structure was very different between studies (last row of Table 2). In the POLA cohort, the estimate of prevalence was based on women over 60 years while in the ESTEV95 cohort, this was based on women aged between 50 and 59 years. The figures in the last column of Table 2 are strongly influenced not only by age but also by the number of studies providing data for each age group and by their relative contribution to the total number of women in each age group. The mean overall prevalence of HT use was 44.3% (Confidence Interval, 95% CI: 43.9–44.7). Data from E3N cohort had the highest influence on

the mean prevalence in the 50–69 years age groups while EPIDOS cohort largely influenced the prevalence 75 years and over. When E3N cohort was not considered, the mean overall estimate of HT use was 22.5% (CI: 21.8–23.2). In the age groups between 65 and 74 years, the sample size was far smaller (500–700 women) and the data only came from OFELY, EVA and above all, POLA cohort (68.5% for the 65–69 years and 51.5% for the 70–74 years age group). Within each age group, prevalence varied widely across cohorts. For instance, in the 60–64 years age group, the prevalence ranged from 17% in OFELY, 18% in POLA, 19% in MONICA to 34% in E3N. In the 65–69 years age group, the prevalence of HT use varied from 5% in OFELY or in POLA to 25% in EVA cohort. Whatever cohorts, the overall prevalence of HT use consistently decreased significantly with age (Chisquare test for trend, 1 d.f., $p<10^{-6}$).

Table 1 **Main characteristics of the eight cohort studies**

| Study | Main objective of the study | Sample size | Population enrolled | Period of enrollment |
|---|---|---|---|---|
| EPIDOS | Osteoporosis epidemiology (prospective cohort study) | 7517 | Electoral roll (Montpellier, Toulouse, Lyon, Paris, Amiens) | 1992–1994 |
| ESTEV95 | Health, work and aging | 7425 | Employees followed by 380 occupational physicians (7 regions) | 1990/1995 |
| EVA | Epidemiology of arterial aging | 469 | Electoral roll (Nantes) | June 1991–June 1993 |
| E3N | Risk factors for cancer and chronic diseases | 98998 | Female members of MGEN health insurance | 1990 |
| GAZEL | Compliance of HT related with information on its indications | 1000 | French public electricity company (Electricité de France, EDF) | 1990–1996 |
| MONICA | Morbidity, mortality and risk factors for cardiovascular diseases | 1730 | Three registers on cardiovascular diseases (Strasbourg, Toulouse, Lille) | 1995–1997 |
| OFELY | Osteoporosis | 1039 | Volunteers among MGEN members | 1992 |
| POLA | Risk factors for cataract and age-related macular degeneration | 1451 | Electoral roll (Sète) | June 1995–July 1997 |

*Standardized prevalence and number of women treated by HT in France*

To estimate the number of women treated by HT in France, we focused our analysis on women aged between 50 and 69 years. The crude and standardized prevalence are reported in Table 3, as well as the estimated number of women treated by HT stratified by 5 years age groups. About 41% of French women aged between 50 and 69 years were estimated to be treated by HT, corresponding to about 2.6 million women. When E3Ncohort was not considered, the standardized prevalence of HT use among women aged 50–69 years old was 36% (35.0; 36.4), corresponding to about 2.2 million women (2,238,042: 2,196,617; 2,279,467), that is to say 12% less than the above estimation (*data not shown*). The standardized prevalence of women treated by HTwas the highest in the age group 50–54 years and these prevalence decreased regularly and significantly across these different age groups (Chi-square test for trend, 1 d.f., $p<10^{-6}$).

*Evolution of HT prescription among menopausal women in France*

Number of women who were reimbursed for HT between November 2002–January 2003 and November 2003–January 2004 are displayed in Table 4. The absolute number of HT users decreased dramatically between the two study periods across all age groups (Chi-square test for trend, 1 d.f., $p<10^{-6}$), from 45% for the 50–54 years age group to 14% for the 65–69 years age group.

**Discussion**

Our study provided estimates on the number of postmenopausal women treated by HT in France prior to the WHI study. We particularly focused on the 50–69 years age group which is the most concerned by HT use [22]. We showed that about 41% of the women aged 50–69 years were treated by HT in France, corresponding to about 2.6 million women. Our results were predominantly based on those of E3N cohort, which over weighted the global finding. Moreover E3N cohort is primarily constituted with a very particular population of school teachers who could not be representative of the overall French postmenopausalwomen [23]. The prevalence of HT use among postmenopausal women is between 36 and 41%, corresponding to 2.2–2.6 million French

women. Finally this prevalence is higher than that previously reported in the Bouches-du-Rhône district among women participating to breast screening campaign (27% among 55–69 years in 1996).

Table 2 **Distribution of hormone therapy's use among women aged over 50 years and enrolled in the eight French cohorts**

| Age group (years) | Study | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | EPIDOS | | ESTEV95 | | E3N | | MONICA | | OFELY | | EVA | | GAZEL | | POLA | | Global (%) |
| | *N* | %HT[a] | *N* | %HT[a] | *N* | %HT[a] | *N* | %HT[a] | *N* | %HT[a] | *N* | %HT[a] | *N* | %HT[a] | *N* | %HT[a] | |
| 50–54[a] | – | – | 1201 | 64.6 | 15758 | 64.9 | 201 | 44.8 | 127 | 43.3 | – | – | 684 | 52.8 | – | – | 64.1 |
| 55–59 | – | – | 1575 | 53.8 | 11820 | 50.5 | 291 | 40.9 | 202 | 36.1 | – | – | 373 | 51.2 | – | – | 50.5 |
| 60–64 | – | – | – | – | 7273 | 33.8 | 325 | 19.4 | 100 | 17.0 | – | – | – | – | 333 | 18.0 | 32.3 |
| 65–69 | – | – | – | – | – | – | – | – | 61 | 4.9 | 110 | 24.5 | – | – | 371 | 4.6 | 8.7 |
| 70–74 | – | – | – | – | – | – | – | – | 89 | 0 | 250 | 14.0 | – | – | 360 | 1.4 | 5.7 |
| 75–79 | 3823 | 7.7 | – | – | – | – | – | – | 79 | 0 | 109 | 11.0 | – | – | 221 | 0.5 | 7.3 |
| 80–84 | 2573 | 6.6 | – | – | – | – | – | – | | – | – | | – | – | 166 | 0 | 6.2 |
| 85–89 | 810 | 5.9 | – | – | – | – | – | – | | – | – | | – | – | | | 5.9 |
| 90+ | 134 | 2.2 | – | – | – | – | – | – | | – | – | | – | – | | | 2.2 |
| Total | 7340 | 7.0 | 2776 | 58.5 | 34851 | 53.5 | 817 | 33.3 | 658 | 22.5 | 469 | 15.8 | 1057 | 52.2 | 1451 | 5.7 | 44.3 |

[a] Hormone therapy.

Table 3 **Estimated numbers of women aged between 50 and 69 years treated with hormone therapy in France**

| Age groups (years) | Crude prevalence (%) | *T*(*s*)[a,b] (%) | 95% CIc of *T*(*s*) (%) | Estimated number of women[d] | 95% CI of estimated number |
|---|---|---|---|---|---|
| 50–54 | 64.1 | 20.3 | [20.0; 20.5] | 401958 | [397551; 406366] |
| 55–59 | 50.5 | 11.2 | [11.3; 15.5] | 154760 | [152245; 157275] |
| 60–64 | 32.3 | 7.3 | [7.1; 7.5] | 106125 | [99611; 106125] |
| 65–69 | 8.7 | 2.1 | [1.5; 2.6] | 30609 | [22261; 38956] |
| 50–69 | 52.3 | 40.8 | [40.1; 41.5] | 2556867 | [2514798; 2589936] |

[a] *T*(*s*): standardized prevalence.
[b] Prevalence after direct standardization among women aged between 50 and 69 years living in metropolitan France (50–54, 55–59, 60–64, 65–69 years groups).
[c] 95% CI: 95% confidence interval.
[d] Estimates based on the number of women aged between 50 and 69 years living in metropolitan France (1999 INSEE census), i.e. 6,267,868; on the number of women aged 50–54 (i.e. 1,984,086), 55–59 (i.e. 1,385,938), 60–64 (i.e. 1,412,859) and 65–69 years (i.e. 1,484,985) living in metropolitan France.

Table 4 **Evolution of the number of menopausal women with reimbursed hormone therapy in the Rhône-Alpes region between November 2002–January 2003 and November 2003–January 2004 (*data from the National Health Insurance Agency of the Rhône-Alpes region*)**

| Age groups (years) | Number of women on hormone therapy | | Δ%[a] | *p*-Value |
|---|---|---|---|---|
| | November 2002–January 2003 | November 2003–January 2004 | | |
| 50–54 | 10249 | 5617 | −44.8 | |
| 55–59 | 20035 | 11980 | −40.1 | |
| 60–64 | 36592 | 25947 | −29.2 | |
| 65–69 | 32518 | 28022 | −13.6 | $<10^{-6}$[b] |
| Total | 99394 | 71566 | −28.3 | |

[a] Δ%: relative variation of hormone therapy reimbursement between both study periods across the four age groups.
[b] Chi-square test for tendency evaluating the distribution of hormone therapy reimbursement between both study periods by the four age groups.

However the authors did not standardize on French national census and the study concerned women aged over 55 years. HT use is known to decrease with age, this is expected to underestimate the prevalence [9]. Kuntz *et al.* [11] provided close estimates of crude prevalence on HT use (49%) from a cohort of 8011 postmenopausal volunteers aged between 45 and 74 years. As there are no register available on HT consumption in France, the numbers of HT users have to be estimated. We based these estimates on eight French cohort studies performed in the 1990s and which included women aged over 50 years. The sample of women analyzed was obtained from heterogeneous sources, not from a stratified representative sample of the population living in France. E3N cohort over weighted the global result since it corresponded to 70.5% of the overall number of considered women. Besides we did not have any information on the types of HT, its indication or duration, although these two parameters are of great importance to assess the appropriateness of these treatments [2]. The cohort studies differed in terms of their objectives, recruitment method, sampling method, selection criteria and geographic location and took place before the availability of WHI's results; the final result obtained when E3N was excluded seem to be more appropriate since the six remaining cohorts are constituted with a panel of various populations, more representative of the French postmenopausal women. On the other hand, the estimated large number of 2.6 million women treated by HT is an indirect proof of better medical follow-up in those women [9] benefiting from a regular gynecological surveillance and earlier medical care when necessary.

The second part of this work aimed to evaluate the impact of WHI's results on HT prescriptions in the Rhône-Alpes region. Between two similar timeperiods, just after WHI's results and 1 year later, HT reimbursements in the Rhône-Alpes region significantly decreased. As data provided the number of HT

reimbursements in 50–69 years old women, we could assume that the first period, November 2002–January 2003, represented HT prescriptions before the WHI's results, since there is a delay between HT prescriptions and individual drug availability then between drug availability and HT reimbursement. We could also assume that the impact of the WHI's results was delayed due to the time for French media to report it in the French women population (first relevant article in December 2002 [22]). The second period truly represented HT prescriptions after the diffusion of WHI's results. The description of women aged 50–69 years old in the Rhône-Alpes region is quite similar from those of the French population (similar proportion of the 50–69 years old age-group, similar proportion of working women) but the part of emigrated women is significantly higher in the Rhône-Alpes region (2.9% versus 2.3%, $p<10^{-6}$) and the distribution of professional category differed also from the global French population (*data obtained from the* 1999 *INSEE census*). The extrapolation of our findings on HT reimbursements should also be interpreted with caution since the Rhône-Alpes region is not well representative from the French population. Moreover we were dependent upon the National Health Agency in the Rhône-Alpes region which only provided data from November 2002, while WHI results were still published. This could probably underestimate the impact of this study on HT prescription if we do not take in account the unknown delay between HT prescriptions and HT reimbursement. The lowest decrease in HT reimbursement after 60 years could be interpret as a higher worry of those women about bone fractures prevention more than a fear to develop breast cancer which is more predominant among women aged between 50 and 59 years old. Since the publication of WHI and MWS's results, HT use has significantly decreased, as noticed in other studies [24,25]. In a French public opinion poll realized in 2004 by the ANAES (*not published*), among 1010 women aged between 45 and 70 years, 29% have stopped definitively or temporarily HT in December 2003, due for 24% to information received on those clinical trials. In parallel, the sales of estrogen and progestogen in France fell down by −16 to 22% in 2003 versus 2002, and this decreased the global healthcare costs by −0.08 to 0.15% [26]. When considering the sales of all drugs in 2003, the global healthcare cost increased by +6% compared to 2002 [27]; this shows that the decrease in HT reimbursement was not linked with a global deficient economy in France but could be specifically attributed to WHI and WMS's impact. Similar results were observed in United States and Canada [28,29], where HT prescriptions of oral estrogen and estrogen/progestogen combinations decreased respectively by 38 and 27% after year 2002. In France, WHI's results have triggered heated discussions and those results were hardly criticized. Extrapolations to the French population were much debated since the study population of WHI was not representative of the French postmenopausal women, in terms of age, prevalence of obesity, way of life, and types of HT [22].

Our study is in keeping with the general pattern of HT use since WHI and MWS's results. In the last 15 years, HT use has increased consistently, particularly in France [29]. Since July 2002 or more truly since October 2003, the indications of HT have been largely reconsidered in France but this only in May 2004 that the French Health Authorities, ANAES and AFSSAPS, edited a public recommendation limiting the indication for HRT to patients with severe climacteric symptoms [3]. The treatment should now be prescribed for the shortest time and at the minimal dose and are now restricted to the relief of menopausal symptoms and in a second intention to the prevention of osteoporosis complications [3]. As the main indications of HT use were not collected for women from the cohort studies, we could not evaluate the appropriateness of the treatment with regard to the recent clinical practices guidelines [3]. The debate is still opened and for the moment numerous points of view exist. The necessity for evaluating the risk of breast cancer in HT users in France is important in order to make a justified decision in the way of prescribing HT. HT demonstrated its efficacy in the prevention of osteoporosis complications [1]. It is now important to evaluate the consequences of WHI's impact in France in terms of bone fractures' incidence and antiosteoporotic treatments' prescriptions. A recent analysis of the National Health Insurance has shown a dramatic increase of antiosteoporotic drugs, especially in primary prevention which represents 40% of the prescriptions, although these treatments are not reimbursed in primary prevention [30].

There is a need for systematic recording of HT use by women in France, in terms of types of treatment in postmenopausal women (estrogen, estrogen/progestogen, tibolone, phytotherapy, etc.), formulation, dose, duration, and this could be collected at every breast cancer screening campaigns, since these programs will be generalized in all French districts in 2007 [31]. These data could be used to estimate over time the number of women treated by HT in France and this number could be compared to data on healthcare products sales provided by the National Institute for Statistics and Economic Studies (INSEE). Only a large randomized clinical

trial evaluating HT used in France would provide quantitative data on the risk-benefit balance and would close the debate on the possible generalization of WHI's results to French HT users.

## Conclusion

We estimated that 2.6 million women aged 50–69 years were treated by HT in France before the publication of WHI and MWS's results. The impact of those clinical trials seemed to exist in France, despite the numerous criticisms on the extrapolation of WHI and MWS to French women. It will be interesting to survey the number of breast cancers and bone fractures but also of antiosteoporotic treatments use and so called "alternative" treatments for menopausal symptoms (e.g., phytotherapy), after the diffusion of recent clinical practices guidelines edited by the French evaluation agencies ANAES and AFSSAPS.

***Acknowledgement***

We are grateful to Dr. Muriel Rabilloud for her methodological input.

## Appendix A

The cohorts identified for our study were the following:

(1) E3N, Etude Epidémiologique de femmes de la MGEN,Unité INSERM XR 521, Gustave Roussy Institute, 94805 Villejuif Cedex, France; study coordinator: Françoise Clavel-Chapelon.
(2) Effets sur la santé de l'exposition aux sous-produits de l'eau,1[1] INSERM U 420, School of Medicine, 54505 Vandoeuvre-lès-Nancy, France; department head: Jean-Marie Mur, study coordinator: Rachel Nadif.
(3) EPIDOS, INSERM U 403, Edouard Herriot Hospital, F Pavillion, 69393 Lyon Cedex 7, France; study coordinators: Gérard Bréart and Pierre Meunier.
(4) ESPRIT1[1], INSERM E 361, 39 avenue Charles Flahault, 34093 Montpellier Cedex, France; research unit director: Karen Ritchie.
(5) ESTEV, évolution des déficiences en fonction de l'âge et des caractéristiques physiques et organisationnelles au cours de la vie active, INSERM U 170, 94807 Villejuif Cedex, France; research unit director: Denis Hémon; study coordinator: Francis Derriennic.
(6) EVA, INSERM U 360, La Pitié-Salpétrière General Hospital, 75651 Paris Cedex 13; research unit director: Annick Alpérovitch; study coordinator: Claudine Berr.
(7) GAPIC,1[1] (Génétique Epidémiologique et moléculaire des pathologies cardiovasculaires), La Pitié-Salpétrière School of Medicine, INSERM U 525, 75634 Paris Cedex 13; research unit director: François Cambien; study coordinator: S. Blankenberg.
(8) Cohorte GAZEL, INSERM U 88, Saint Maurice National Hospital, 94415 Saint Maurice Cedex, France; research unit director: Marie Zins.
(9) "Les femmes dans la ville": épidémiologie en santé périnatale et santé des femmes, INSERM U 149, Tenon Hospital, 75970 Paris Cedex 20, France; research unit director: Gérard Bréart.
(10) Mastopathies bénignes et risque de cancer du sein,1[1] INSERM U 521, Gustave Roussy Institute, 94805 Villejuif Cedex, France; research unit director: Catherine Bonaïti; study coordinator: Monique Le.
(11) MONICA, INSERM U 258, Paul Brousse Hospital, 94807 Villejuif Cedex, France; research unit director: Pierre Ducimetière.
(12) OFELY, INSERM U 403, Edouard Herriot Hospital, F Pavillion, 69393 Lyon Cedex 7, France; research unit director: Pierre Dominique Delmas.
(13) PAQUID, INSERM U 330, Victor Ségalen University, 33076 Bordeaux Cedex, France; research unit director: Roger Salamon; study coordinator: Jean-François Dartigues.
(14) POLA, INSERM U 500, 34093 Montpellier Cedex 05, France; research unit director: Laure Papoz; study coordinator: Cécile Delcourt.
(15) SU VI MAX Study (SUpplémentation en Vitamines et Minéraux AntioXidants), Institut Scientifique et Technique de la Nutrition et de l'Alimentation, 75003 Paris; principal investigator: Serge Hercberg.
(16) Health Insurance Database, Regional National Health Insurance Agency, 69436 Lyon Cedex 03, France; head physicians: Joelle Guilhot and Roland Nublat; statistician: Valérie Tainturier.

[1] Studies not included in our work.

***References***

[1] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women JAMA 2002;288:321–3.

[2] Million Women Study Collaborators,. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.

[3] Agence Nationale d'Accréditation et d'Evaluation en Santé. Traitements hormonaux substitutifs de la ménopause. *Rapport d'orientation 11 mai 2004*. Paris: ANAES; 2004.

[4] Bundesinstitut für Arzneimittel und Medizinprodukte. Estrogen-und Estrogen-Gestagen-haltige Arzneimittel zur Hormonsubstitution. Available at: http://www.bfarm.de/de/arzneimittel/am_sicher/am_sicher_akt/hrt_bescheid.pdf Accessed August 31, 2004.

[5] Gordon D, Committee of safety Medicines. Further advice on safety of HRT: risk:benefit unfavourable for first-line use in prevention of osteoporosis. Available at: http://www.mca.gov.uk. CEM/CMO/2003/19. Accessed August 31, 2004.

[6] Rymer J,Wilson R, Ballard K. Making decisions about hormone replacement therapy. BMJ 2003;326:322–6.

[7] Nagata C, Matsushita Y, Shimizu H. Prevalence of hormone replacement therapy and user's characteristics: a community survey in Japan. Maturitas 1996;25:201–7.

[8] World Population Projections, HRT Market Penetration 1999 (IMS data). Novo Nordisk; 2000.

[9] Séradour B, Estève J, Heid P, et al. Hormone replacement therapy and screening mammography: analysis of the results in the Bouches-du-Rhône programme. J Med Screening 1999;6:99–102.

[10] Ringa V. Traitement hormonal substitutif de la ménopause. Le point épidémiologique en 2002. Actualité et dossier en santé publique 2002;38:18–21.

[11] Kuntz C, Spyckerelle Y, Giordanella JP. Caractéristiques des femmes sous traitement hormonal substitutif de la ménopause: étude descriptive dans la population fréquentant les Centres d'examens de santé. BEH 2004;7:25–6.

[12] Amamra N, Berr C, Clavel-Chapelon F, et al. Estimated number of women likely to benefit from bone mineral density measurement in France. Joint Bone Spine 2004;71:409–18.

[13] Lascaux-Lefebvre V, Ruidavets J, Arveiler P, et al. Influence of parental history of hypertension on blood pressure.HumHypertens 1992;13:631–6.

[14] Ringa V, Ledesert B, Breart G. Determinants of replacement therapy among postmenopausal women enrolled in the French GAZEL cohort. Osteoporosis Int 1994;4:16–20.

[15] Derriennic F, Touranchet A, Volkoff S, editors. Age-Travail-Santé; Etudes sur les salariés âgés de 37 à 52 ans, enquête ESTEV 1990. Paris: Editions INSERM; 1996 Questions en Santé Publique.

[16] Clavel-Chapelon F, Jadand C, Goulard H, et al. E3N a cohort study on cancer risk factors in MGEN women. Description of protocol, main characteristics population. Bull Cancer 1996;8:1008–13.

[17] Arlot ME, Sornay-Rendu E, Garnero P, et al. Apparent prepostmenopausal bone loss evaluated by DXA at different skeletal sites in women: the OFELY cohort. J Bone Miner Res 1997;12:683–90.

[18] Schott AM, Cormier C, Favier F, et al. How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporosis Int 1998;8:247–54.

[19] Delcourt C, Diaz JL, Ponton-Sanchez A, et al. Smoking and age-related macular degeneration: the POLA Study. Arch Ophtalmol 1998;116:1031–5.

[20] Gourlet V, Verdier-Taillefer MH, Berr C. Traitement hormonal substitutif chez les femmes de plus de 60 ans (cohorte EVA): analyse descriptive et étude des relations avec le fonctionnement cognitif. Année Gérontologique 2000:174–86.

[21] Breslow NE, Day NE. Statistical methods in cancer research. Volume II. The design and analysis of cohort studies, no. 82. IARC Scientific Publications; 1987.

[22] De Lignières B, de Vathaire F, Fournier S, et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3,175 women. Climacteric 2002;5:332–40.

[23] Fournier A, Berrino F, Riboli E, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005;114:448–54.

[24] Ettinger B, Grady D, Tosteson ANA, et al. Effect of the Women's Health Initiative on women's decisions to discontinue postmenopausal hormone therapy. Obstet Gynecol 2003;102:1225–32.

[25] Fournier A, Hill C, Clavel-Chapelon F. Hormone replacement therapy and breast cancer risk. Bull Cancer 2003;90:821–31.

[26] Amar E. Les dépenses de médicaments remboursables en 2003. Une contribution renforcée des produits nouveaux. Available at: http://www.sante.gouv.fr/drees/etude-resultat/er-pdf/er324.pdf. Accessed August 30, 2004.

[27] Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy. JAMA 2004;291:47–53.

[28] IMS Health Canada. HRT prescriptions fall by nearly one-third. Available at: http://www.imshealthcanada.com/htmen/1 0 13.htm. Accessed August 30, 2004.
[29] Ringa V, Jaussent I, Guégen R, et al. Trends in the use of hormone therapy in eastern France between 1986 and 1993. Eur J Publ Health 1999;9:300–5.
[30] Ostéoporose: étude des prescriptions des biphosphonates et du raloxifène. Available at: http://www.ameli.fr/244/doc/1462/article.html. Accessed April 9, 2005.
[31] Mission Interministérielle pour la Lutte contre le Cancer. Plan Cancer: 2003–2007. Available at: http://sante.gouv.fr/htm/dossiers/cancer/plaquette_cancer.pdf. Accessed August 31, 2004.