Postmenopausal hormone therapy initiation before and after the Women's Health Initiative in two French cohorts Running title: Evolution of HT use in France

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Running title: Evolution of HT use in France

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Abstract

Objectives. To describe the evolution after the release of the first results from the Women's Health Initiative trial (July 2002) of hormone therapy initiation among newly postmenopausal women.
Methods. We used data from two French prospective cohorts, E3N and Gazel. We identified 3,364 women with natural menopause onset occurring before year 2002; and 1,880 women with menopause onset occurring after year 2002.
Results. After year 2002, the age-standardized rate of hormone therapy initiation (no later than one year following menopause onset) in newly postmenopausal women fell by 69.9% (67.9% and 74.8% in the E3N and Gazel cohorts, respectively). There were also changes in the distribution of both the route of administration of estrogen and the type of associated progestagen, which made transdermal estrogen plus progesterone the largely predominant HT type initiated after year 2002 (43.6% of the initiated HT -- 44.0% and 42.2% in the E3N and Gazel cohorts, respectively).
Conclusions. The evolution of hormone therapy initiation was similar in these two French cohorts, with a substantial drop in HT initiation rate accompanied by changes in the types of hormone therapy used.

Key words: cohort studies; estrogens; hormone therapy; menopause; progestogens; France

Introduction

July 2002 represented the start of a "new era" for postmenopausal hormone therapy (HT), with the publication of the first results from the Women's Health Initiative (WHI) trial.[1] While HT was largely considered beneficial up to the end of the 1990s,[2] concerns of cardiovascular safety demonstrated by this trial together with the reports of an increased breast cancer risk among estrogen plus progestogen therapy (EPT) users[1;3] led the European Medicines Agency to restrict indications of HT to the treatment of climacteric symptoms.[4] Rapid and substantial decreases in HT use were observed in a number of countries, including France.[5;6] These declines resulted from treatment discontinuations and from rejection of initiating treatment in newly postmenopausal women. In France, the specific contribution of the latter is not known. We also lack information on whether the decrease in use was accompanied by changes in the types of HT prescribed. We used data from two French cohort studies to investigate these issues.

Methods

The cohorts

E3N is a prospective cohort that consists of 98,995 French women born between 1925 and 1950 and insured with a national health insurance scheme primarily covering teachers. Women were enrolled in 1990 when they replied to a self-administered questionnaire and gave written informed consent; follow-up questionnaires were sent every 2-3 years.

The GAZEL cohort is composed of employees of the French national power company, Electricité de France-Gaz de France (EDF-GDF), who volunteered to participate in medical research.[7] Within this cohort, a prospective survey of health during the pre-, peri-, and postmenopausal periods began in 1990. It included all women cohort members aged 45 years or older in 1990 and subsequently added those who turned 45 the preceding year. Women in this subcohort received a self-administered questionnaire every three years.

In both cohorts, collected data included menopausal status and use (current and past) of hormonal treatments, as detailed elsewhere.[8;9]

Definition of menopause, HT initiation and periods compared

Women were considered naturally postmenopausal if they reported amenorrhea for more than one year, unless due to hysterectomy or oophorectomy, or if they had ever used HT (and had begun their treatment more than a year earlier, in the Gazel cohort) in the absence of oophorectomy or hysterectomy. In the E3N cohort, natural menopause also included women who declared that they were naturally postmenopausal. In the Gazel cohort, women who had a hysterectomy without oophorectomy before menopause were also considered naturally menopausal if menopause was confirmed by hormone assays. In both cohorts, age at natural menopause was defined as age at last menstrual period, except when cessation of menstruation was due to hysterectomy or when HT use preceded the permanent cessation of menstruation. In the case of an unknown age at last menstrual period, the self-reported age at menopause was used instead. In the Gazel cohort, when HT use preceded the permanent cessation of menstruation, age at menopause was set at age at HT start.

A woman was considered a HT initiator if, one year after menopause onset, she had ever used HT. HT included any systemic use of estrogens (alone or combined with a

progestogen); vaginally administered estrogens were not considered as HT. In case of treatment switch during follow-up, only the first HT used was considered.
In the E3N cohort, we compared HT initiation among women who became postmenopausal between July 1999 and July 2001 (*i.e.* before the release of the first WHI results, in July 2002, with a one-year gap allowing the identification of HT initiators among women with menopause onset in July 2001) to HT initiation among those who became postmenopausal between January 2003 and December 2005 (*i.e.* after the release of the first WHI results, with a 6-month gap allowing results to spread among women and practitioners). In the Gazel cohort, the first period was extended to January 1994-July 2001 to reach more satisfactory numbers; the second period was January 2003-December 2007. In the following, we will refer to these periods as "pre-WHI" and "post-WHI".

Populations for analysis
From the naturally postmenopausal women, we selected 3,611 women for study in the E3N cohort (2,251 with menopause onset in the pre-WHI period and 1,360 in the post-WHI period) and 1,633 women for study in the Gazel cohort (1,113 with menopause onset in the pre-WHI period and 520 in the post-WHI period) (Figure 1). Of note, because women in the E3N cohort are born between 1925 and 1950 and because in the post-WHI population menopause onset should have occurred in January 2003 or later, the minimum age at menopause can not be less than 52 years old. Likewise, as women in the Gazel cohort are born between 1939 and 1953, the minimum age at menopause can not be less than 49 years old.

Statistical methods
Because the pre-WHI and post-WHI sets of women had different age structures, rates of HT initiation were compared using age standardization, women with menopause onset in the pre-WHI period serving as the standard population (using 1-year categories). Percentages were compared using bilateral Chi-Square tests.

Results
Selected characteristics of women included in the analysis are shown in Table 1.
In the pre-WHI period, 55.8% (58.2% and 51.1% in the E3N and Gazel cohorts, respectively) of the newly postmenopausal women initiated HT; in the post-WHI period, the age-standardized rate of HT initiation was 16.8% (18.7% and 12.9% in the E3N and Gazel cohorts, respectively). After year 2002, the age-standardized rate of HT initiation therefore fell by 69.9% (67.9% and 74.8% in the E3N and Gazel cohorts, respectively).
Table 2 shows the distribution of the types of HT initiated in the pre- and post-WHI periods. In both cohorts, transdermal estrogens, already used by the majority before year 2002, became even more used after year 2002 (Table 2). Women initiating transdermal estrogen therapy in the post-WHI compared with the pre-WHI period used significantly more frequently progesterone as the progestogen component (68.0% vs. 40.3% of transdermal EPT initiators -- 67.6% vs. 40.9% and 69.2% vs. 39.0% in the E3N and Gazel cohorts, respectively). We were not able to detect any substantial change in the distribution of the progestogen molecule associated with oral estrogens. While the transdermal estrogen plus progesterone combination represented 21.9% of the initiated HT in the pre-WHI period (22.5% and 20.6% in the E3N and Gazel cohorts, respectively), it became the largely

predominant HT type initiated in the post-WHI period (43.6% of the initiated HT -- 44.0% and 42.2% in the E3N and Gazel cohorts, respectively).

Discussion

In these two French cohort studies, in spite of different participant's characteristics (see Table 1), we observed close figures for the evolution of HT initiation between the pre- and the post-WHI periods. There was an approximately 70% drop in the rate of HT initiation in newly postmenopausal women and a doubling in the proportion of HT initiators using transdermal estrogens associated with progesterone.

Data from the reimbursement databanks of the French National Health Fund showed that the prevalence of HT use approximately halved between 2000 and 2005.[10] Our study suggests that the drop in the rate of HT initiation in newly postmenopausal women is even stronger.

The WHI trial evaluated oral conjugated equine estrogens associated with medroxyprogesterone acetate. In France, there is a widespread use of transdermal estradiol, and a wide range of progestagens is prescribed. This originates from the 1980s and 1990s with the strong influence of a prestigious research-oriented Parisian hospital service, which notably conducted a pioneering work on percutaneous administration of sex hormones.[11] Even before year 2003, conjugated equine estrogens have been only marginally used and medroxyprogesterone acetate has been rarely prescribed in association with transdermal estrogens.[8]

The increasing popularity of the transdermal estrogen plus progesterone combination we observed in the post-WHI period is likely explained by the release in 2003-2004 of the results from two French studies. In 2003, the first one suggested that transdermal HT is safer than oral HT with respect to thrombotic risk[12] and in 2004 (online publication), the E3N study suggested that progesterone may be preferred to other progestagens in short-term HT with respect to breast cancer risk.[13] There is a paucity of studies with a sufficient follow-up duration after year 2002 to evaluate whether these results may have influenced HT prescriptions elsewhere, especially in the United States. In the months following July 2002, smaller declines in prescriptions were observed for HT other than the one evaluated in the WHI trial, including for transdermal formulations.[14] To our knowledge, only two American studies reported on the evolution beyond year 2003 of the types of HT prescribed. Based on prescription data from the United States Military health care system in Hawaii, Parente *et al.* observed a smaller decline for estradiol patches than for oral HT during the period July 2002 to July 2005.[15] A study examining the number of HT prescriptions filled in a health maintenance organization however found that the rate of transdermal estrogens prescribed to HT initiators remained stable across the period August 2002 to December 2004, but these results were based on very low numbers.[16] It is therefore unclear whether a shift in the route of administration of HT has also occurred in the United States after year 2003. We found no study reporting on the evolution of the progestagen molecules used in combined HT.

Differences in the lengths of follow-up in the pre- and post-WHI periods between the E3N and the Gazel cohorts may explain slight differences in the distribution of the specific EPT types between the two cohorts. However, to our knowledge, there has been no marked variation in HT availability susceptible to explain for the differences we observed before and after the WHI. Gels or patches of estrogens have been available during our entire study period, as well as progesterone, a

variety of progesterone- and testosterone-derivatives, and combinations of oral estrogen and progesterone- as well as testosterone-derivatives. The only notable change was that a transdermal combination of estrogen and testosterone derivatives was for the first time marketed in year 2001. From the end of year 1993, almost all HT were equally reimbursed.
The rates of HT initiation we observed may not be applicable to the general population due to the specific characteristics of our participants, who may also be especially health conscious as they volunteered to participate in a medical research project. However, time trends as well as types of treatments used are more likely to reflect prescription habits at a national level.

Conclusions
Evolution of HT initiation was similar in these two French cohorts, with a substantial drop in HT initiation rate in newly postmenopausal women accompanied by changes in the types of hormone therapy used. There is a paucity of studies evaluating to what extent similar shifts in the types of HT used have occurred outside France, especially in the United States.

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Figure 1. Selection of the pre-WHI and post-WHI populations. Number of women is indicated as "n" (number of women from the E3N cohort / number of women from the Gazel cohort).

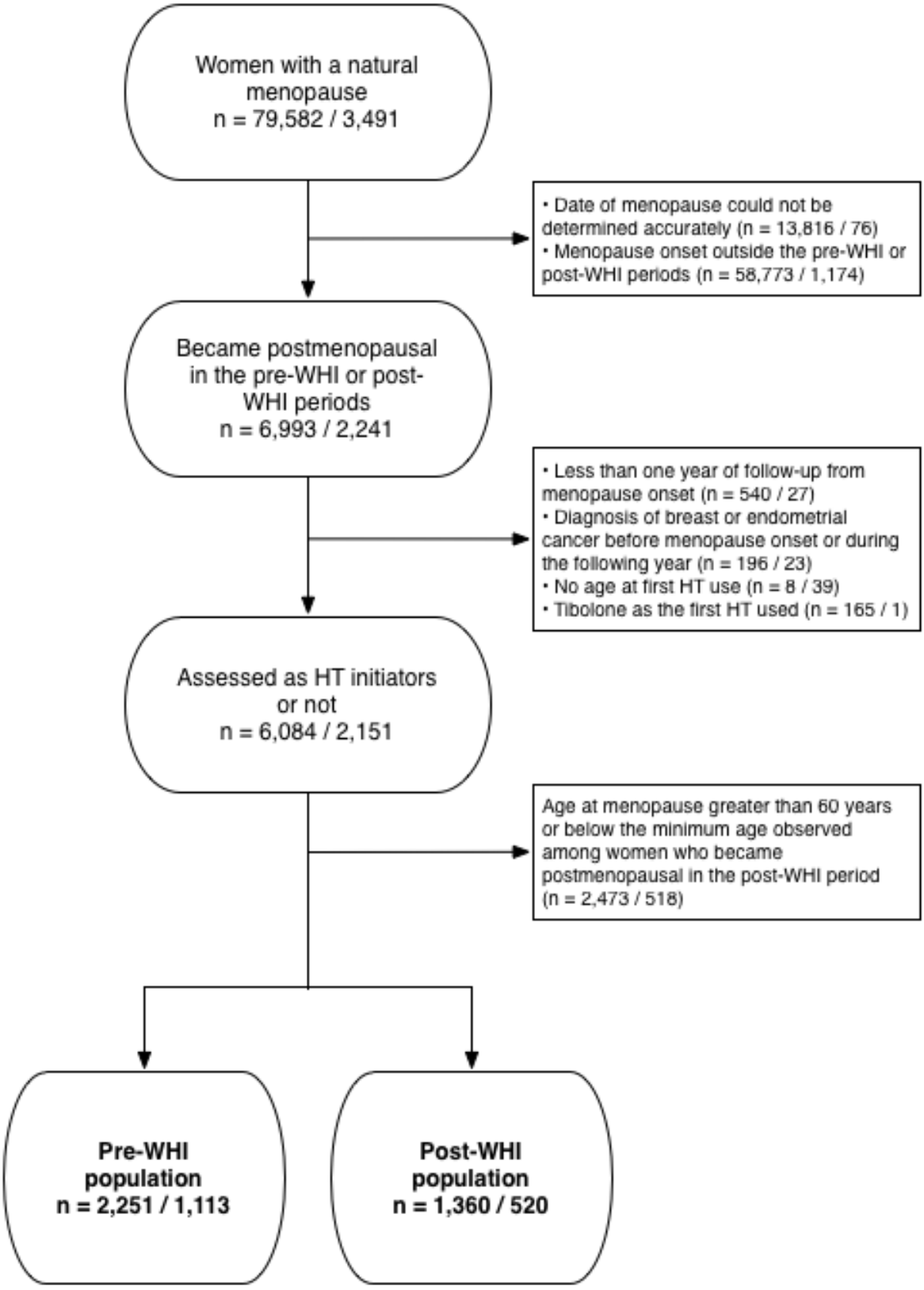

Table 1. Selected characteristics of included women *

	E3N cohort (n = 3,611)	Gazel cohort (n = 1,633)	E3N and Gazel combined (n = 5,244)
Age at menopause among women with menopause onset in the pre-WHI period			
Mean	54.3	52.2	53.6
Standard deviation	1.35	1.95	1.86
Range	52.6 to 59.9	49.4 to 59.6	49.4 to 59.9
Age at menopause among women with menopause onset in the post-WHI period			
Mean	55.1	53.3	54.6
Standard deviation	1.36	1.92	1.73
Range	52.7 to 60.0	49.4 to 59.0	49.4 to 60.0
Years of schooling			
<12	271 (7.5)	1,222 (74.8)	1,493 (28.5)
12-14	1,759 (48.7)	268 (16.4)	2,027 (38.7)
15+	1,581 (43.8)	109 (6.7)	1,690 (32.2)
Missing	0	34 (2.1)	34 (0.6)
Body Mass Index (kg/m^2)			
<18.5	176 (4.9)	42 (2.6)	218 (4.1)
18.5-24.9	2,524 (69.9)	1,099 (67.3)	3,623 (69.1)
25-29.9	719 (19.9)	325 (19.9)	1,044 (19.9)
30+	192 (5.3)	123 (7.5)	315 (6.0)
Missing	0	44 (2.7)	44 (0.8)
Marital status			
Alone	682 (18.9)	382 (23.4)	1,064 (20.3)
With a partner	2,929 (81.1)	1,251 (76.6)	4,180 (79.7)
Nulliparous			
Yes	337 (9.3)	139 (8.5)	476 (9.1)
No	3,274 (90.7)	1,465 (89.7)	4,739 (90.4)
Missing	0	29 (1.8)	29 (0.6)
Ever use of oral contraceptives			
Yes	2,859 (79.2)	1,336 (81.8)	4,195 (80.0)
No	752 (20.8)	289 (17.7)	1,041 (19.9)
Missing	0	8 (0.5)	8 (0.2)

* Data are presented as n (%) unless otherwise specified

Table 2. Types of systemic HT initiated in the pre- and post-WHI periods in two French cohorts

	E3N cohort		Gazel cohort		E3N and Gazel combined		
	HT initiated in the pre-WHI period n (%*)	HT initiated in the post-WHI period n (%*)	HT initiated in the pre-WHI period n (%*)	HT initiated in the post-WHI period n (%*)	HT initiated in the pre-WHI period n (%*)	HT initiated in the post-WHI period n (%*)	p for homogeneity of %
Oral estrogens	**461 (41.3%)**	**58 (26.6%)**	**233 (40.9%)**	**14 (21.9%)**	**694 (41.2%)**	**72 (25.5%)**	**<.001**
Alone	7	0	7	1	14	1	
Combined	454	58	226	13	680	71	
+ *progesterone*	*27 (5.9%)*	*2 (3.4%)*	*22 (9.7%)*	*2 (15.4%)*	*49 (7.2%)*	*4 (5.6%)*	*0.6*
+ *progesterone-derivatives†*	*315 (69.4%)*	*41 (70.7%)*	*170 (75.2%)*	*7 (53.8%)*	*485 (71.3%)*	*48 (67.6%)*	*0.5*
+ *testosterone-derivatives‡*	*112 (24.7%)*	*15 (25.9%)*	*34 (15.0%)*	*4 (30.8%)*	*146 (21.5%)*	*19 (26.8%)*	*0.3*
Transdermal estrogens	**654 (58.7%)**	**160 (73.4%)**	**336 (59.1%)**	**50 (78.1%)**	**990 (58.8%)**	**210 (74.5%)**	**<.001**
Alone	40	18	36	11	76	29	
Combined	614	142	300	39	914	181	
+ *progesterone*	*251 (40.9%)*	*96 (67.6%)*	*117 (39.0%)*	*27 (69.2%)*	*368 (40.3%)*	*123 (68.0%)*	*<.001*
+ *progesterone-derivatives†*	*337 (54.9%)*	*35 (24.6%)*	*177 (59.0%)*	*11 (28.2%)*	*514 (56.2%)*	*46 (25.4%)*	*<.001*
+ *testosterone-derivatives‡*	*26 (4.2%)*	*11 (7.7%)*	*6 (2.0%)*	*1 (2.6%)*	*32 (3.5%)*	*12 (6.6%)*	*0.05*
Total¶	**1,115**	**218**	**569**	**64**	**1,684**	**282**	

Abbreviations: HT, hormone therapy; WHI, women's health initiative

* For the detailed estrogen plus progestogen combinations, the denominator of the % is the number of estrogen plus progestogen initiators with the considered route of estrogen administration; otherwise, the denominator of the % is the total number of HT initiators.

† Progesterone-derivatives include medrogestone, chlormadinone acetate, cyproterone acetate, medroxyprogesterone acetate, nomegestrol acetate, demegestone and promegestone

‡ Testosterone-derivatives include levonorgestrel, norethisterone acetate, lynestrenol, gestodene, dienogest and drospirenone

§ Excluding HT initiators with type of progestogen or route of administration of estrogen not specified (*n* = 194 in E3N women who initiated HT in the pre-WHI period; *n* = 31 in E3N women who initiated HT in the post-WHI period; n = 0 in Gazel women)