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► **To cite this version:**

Séverine Sabia, Agnès Fournier, Sylvie Mesrine, Marie-Christine Boutron-Ruault, Françoise Clavel-Chapelon. Risk of onset of menopausal symptoms in periods surrounding menopause.. *Maturitas*, 2007, 58 (4), pp.340-7. 10.1016/j.maturitas.2007.09.012 . inserm-00192649

**HAL Id: inserm-00192649**

**<https://inserm.hal.science/inserm-00192649>**

Submitted on 29 Nov 2007

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# Risk of onset of menopausal symptoms in periods surrounding menopause

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## Abstract

*Objective:* To assess the risk of onset of menopausal symptoms at different periods surrounding menopause, and variations in this risk according to age at menopause and type of menopause.

*Methods:* We analyzed the 27,897 women participating in the French E3N cohort study who reached menopause during a 10-year follow-up period (1990–2000). Self-administered questionnaires, completed approximately every 24 months, included questions on the use of hormonal treatments, reproductive factors, personal history of a variety of diseases and the occurrence of personal medical events, including menopausal symptoms. Hazard ratios (HRs) were computed from multivariate Cox models.

*Results:* When compared to the year preceding menopause, the risk of onset of menopausal symptoms was higher in the year following menopause (for natural menopause ( $n = 25,753$ ), HR= 1.22, 95% confidence interval: 1.17, 1.27, and for artificial menopause ( $n = 2,147$ ), HR= 2.21, 95% CI: 1.93, 2.52). More than one year prior to menopause and more than one year after, HRs were significantly below unity. The risk of onset of menopausal symptoms in the year following menopause was 1.47-fold (95% CI: 1.31, 1.64) higher in women having undergone an artificial menopause than in women who had had a natural menopause. In other periods, the risks did not differ significantly according to type of menopause. Those who experienced menopausal symptoms in the 1–5 year period following menopause were more likely to have reached their menopause before 51 years.

*Conclusions:* The risk of onset of menopausal symptoms at different time periods surrounding menopause varies according to both type of menopause and age at menopause.

*Keywords:* Menopausal symptoms; Artificial and natural menopause; Age at menopause

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## Introduction

Menopause, or permanent cessation of ovarian activity, is part of normal aging. At least in Western countries, most women experience menopausal symptoms [1]. These may occur before or after the onset of menopause. Studies on the prevalence of menopausal symptoms during menopausal transition have reported that these were more likely to be experienced in late menopausal transition and in early postmenopause [2–12]. However, the main methodologic issues that limit inferences from epidemiologic studies of the menopausal transition are lack of longitudinal studies and short follow-up [5,13]. Another limitation is that few studies include surgical menopause cases [2,4,14]. Moreover, later age at menopause was associated with a decrease in the risk of occurrence of hot flushes and vaginal dryness in some studies [14,15], but it remains unclear whether the onset of menopausal symptoms varies across different time periods of menopausal transition according to age at menopause.

Using data from the large E3N (Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale) cohort study [16], we evaluated whether the risk of onset of menopausal symptoms varied according to (i) different time periods surrounding menopause, (ii) type of menopause and (iii) age at menopause. We further examined the risk of onset of menopausal symptoms according to age at menopause in different time periods surrounding menopause.

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## Methods

### *Population*

E3N is a French prospective study investigating cancer risk factors in 98,995 women born between 1925 and 1950. All women belong to a health insurance system primarily covering teachers. All study subjects signed an informed consent form in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (Commission Nationale Informatique et Libertés) from which we obtained approval. Part of the E3N cohort (i.e. those who replied to a dietary questionnaire) is also included in the European Prospective Investigation into Cancer and Nutrition (EPIC) [17].

### *Assessment of information*

Since June 1990, participants have been requested at approximately 24-month intervals to complete self-administered questionnaires recording information on lifestyle characteristics, reproductive factors and medical history. Information on date of menopause, type of menopause, date of last menstruation, date of unilateral or bilateral oophorectomy or hysterectomy were recorded at baseline and updated in each of the five subsequent questionnaires (the last to be taken into account for the present study was sent out in June 2000). Natural menopause was defined retrospectively after 12 consecutive months without natural menstrual periods [1], and age at menopause was the age at last menstruation or the self-reported age at menopause in case of prior hysterectomy without bilateral ovariectomy. Artificial menopause was defined as the cessation of menstruation following either surgical removal of both ovaries (with or without hysterectomy) or iatrogenic cessation of ovarian function (e.g., chemotherapy or radiation). The accuracy of self-reported menopausal status (premenopausal or postmenopausal) and age at menopause at baseline has been analysed in a validation study using the gynecologist's medical records as Ref. [18]. Concordance between women response at the baseline questionnaire and medical records was assessed in 151 women. The kappa coefficient obtained for menopausal status was 0.85 (95% CI: 0.69–1.00). Agreement on age at menopause was tested in the 57 postmenopausal women and the kappa coefficient obtained was 0.64 (95% CI: 0.34–0.94). Age at menopause within 1 and 2 years was accurately reported by 69 and 86%, respectively.

Eight periods characterizing menopausal transition were defined according to the menopause-related time interval: ]0–1[, [1–3[, [3–5[ and more than 5 years prior to menopause, and [0–1[, [1–3[, [3–5[ and more than 5 years after menopause.

Information on menopausal symptoms were derived from the following question “Are you experiencing (or have you ever experienced) menopausal symptoms (hot flashes, etc.)?” included in each of the five follow-up questionnaires. So, women could report hot flashes as well as others symptoms that she felt in relation with menopause. Women were further asked to provide the date of the onset of menopausal symptoms. No information was recorded on the type of menopausal symptoms the women experienced.

### *Study design*

We analyzed data on women who had reached menopause after 1990 (start of follow-up) and before June 2000 (end of follow-up), and who had given all details concerning the circumstances of their menopause (age and type of menopause, and age of onset of menopausal symptoms if they had declared having experienced some). Among these 29,546 women, we excluded women who reported having experienced menopausal symptoms before the start of follow-up ( $n = 1266$ ). These criteria were chosen in order to limit recall bias regarding central parameters (age at menopause and age at onset of menopausal symptoms). Phytoestrogen users ( $n = 383$ ) were also excluded because these treatments might alter the risk of menopausal symptoms (including a possible placebo effect) [19]. A total of 27,897 women with a mean age at the start of follow-up of 45.8 years (standard deviation (S.D.) = 3.5) were thus included in this analytical study.

### *Statistical analysis*

Hazard ratios (HR) and 95 % confidence intervals (CI) of onset of menopausal symptoms were estimated using Cox proportional hazards models that take censoring into account, adjusted for parameters shown to be potential risk factors for menopausal symptoms [2,3,14,15] or to influence the onset of menopause [2,20–23] as indicated in footnotes to Table 1.

Each woman contributed person-years from the date of the baseline questionnaire until the date of onset of menopausal symptoms, date of start of use of hormone replacement therapy (HRT) (as use of HRT may mask the onset of menopausal symptoms), or end of follow-up, whichever occurred first.

First we calculated the HRs according to categories of time period surrounding menopause defined above, with the year preceding menopause as the reference category. Secondly, we compared the risk of onset of menopausal symptoms following artificial menopause to that following natural menopause. In these two first analyses, age was chosen as the time scale to control for its effects. Then, we examined the risk of onset of menopausal symptoms according to age at menopause. As age at menopause was included in the model, time since menopause (or time to menopause) was chosen as the time scale, to overcome the fact that age at menopause can be derived from the time since menopause and the age. Finally, in order to examine whether the effect of age at menopause varied in different periods surrounding menopause, we calculated HRs according to age at menopause in analyses stratified on time periods surrounding menopause.

Sensitivity analysis was performed, excluding women who had used contraceptive pills or progestogens during follow-up; estimates did not change appreciably and are therefore not presented here.

Wald tests were performed to compute  $p$ -values. All tests of significance were two-sided. All analyses were performed using SAS Software, Version 9.1.

## Results

During a mean duration of follow-up of 5.5 years (S.D. = 3.0), 16,278 (58.4%) of the 27,897 women included in the analysis reported menopausal symptoms, which appeared at a mean age of 50.3 years (S.D. = 2.9). The mean age at natural menopause ( $n = 25,753$ ) was 51.3 years (S.D. = 2.7) and the mean age at artificial menopause ( $n = 2144$ ) was 50.0 (S.D. = 3.0).

### *Risk of onset of menopausal symptoms according to the time period surrounding menopause*

HRs of onset of menopausal symptoms among women with natural and artificial menopause are shown in Table 1. Since crude HRs were of similar magnitude, only multivariate HRs were presented. As compared to the year preceding menopause, considered as the reference period, the risk of onset of menopausal symptoms was higher in the year following menopause. This was true for both women who underwent natural menopause (HR = 1.22, 95% CI: 1.17, 1.27) and women with an artificial menopause (HR = 2.21, 95% CI: 1.93, 2.52). More than 1 year before menopause and more than 1 year after, HRs were significantly below unity.

Tests for interaction were performed between confounding variables and periods surrounding menopause; none was significant.

### *Risk of onset of menopausal symptoms according to type of menopause*

The risk of onset of menopausal symptoms after menopause was statistically higher in women who had undergone an artificial menopause than in women having had a natural menopause (HR = 1.16, 95% CI: 1.04, 1.28), particularly in the year following menopause (HR = 1.47, 95% CI: 1.31, 1.64). During other time periods, it did not differ significantly.

### *Risk of onset of menopausal symptoms according to age at menopause*

HRs were also calculated according to the following age at menopause categories: < 49, [49–51[, [51–53[, and  $\geq 53$ .

Overall, when menopause was natural, HRs of onset of menopausal symptoms did not differ significantly across ages at menopause < 49, 49–51, and 51–53 years ( $p$  of homogeneity = 0.16). In contrast, women who reached menopause after the age of 53 were at decreased risk of menopausal symptoms compared to those who had reached menopause earlier (HR = 1.05, 95% CI: 1.01, 1.11, HR = 1.05, 95% CI: 1.01, 1.10, and HR = 1.06, 95% CI: 1.02, 1.11, for categories of age at menopause of <49, 49–51 and 51–53 years, respectively, compared to  $\geq 53$  years).

Experiencing an artificial menopause between 40 and 51 years compared to after 51 years was associated with a higher risk of onset of menopausal symptoms (HR = 1.70, 95% CI: 1.27, 2.29, HR = 1.50, 95% CI: 1.09, 2.06, and HR = 1.05, 95% CI: 0.69, 1.61; for age at menopause < 49, 49–51 and  $\geq 53$  years, respectively, compared to 51–53 years,  $p$  for trend = 0.01).

**Table 1 Hazard ratios (HR)<sup>a</sup> and 95 % confidence intervals (CI) of onset of menopausal symptoms in periods surrounding menopause stratified by type of menopause, E3N, French cohort, 1990–2000**

	Natural menopause (n= 25,753)				Artificial menopause (n= 2,144)			
	Number of cases	Person-years	HR	95% CI	Number of cases	Person-years	HR	95% CI
Years before menopause								
5+	281	36722	0.03	0.03, 0.04	15	2430	0.03	0.02, 0.05
[3-5[	816	32496	0.09	0.08, 0.10	51	2466	0.09	0.06, 0.12
[1-3[	3896	38080	0.33	0.32, 0.35	171	3212	0.21	0.17, 0.25
]0-1[	5546	17028	1 (ref)		433	1634	1 (ref)	
Years after menopause								
]0-1[	3606	7615	1.22	1.17, 1.27	464	536	2.21	1.93, 2.52
[1-3[	847	5693	0.49	0.46, 0.53	49	371	0.51	0.38, 0.68
[3-5[	76	2614	0.12	0.10, 0.15	7	220	0.14	0.06, 0.29
5+	16	2351	0.04	0.03, 0.07	4	206	0.10	0.04, 0.26

<sup>a</sup>Cox models with age as the time scale, further adjusted for years of schooling (<12, 12–14, ≥15), alcohol consumption (quartiles, as reported in the dietary questionnaire in 1993), energy intake (<1800, 1800–2500, >2500 kcal/day as reported in the dietary questionnaire in 1993), number of children (0, 1, 2, ≥3), age at menarche (<12, 12, 13, 14, >14 years), physical activity (quartiles), usual (i.e. excluding perimenopause and periods of oral contraceptive use), duration of menstrual cycles (<25, 25–31, >31 days, irregular), smoking status (as a time-dependent variable: current, past, never), body mass index (as a time-dependent variable: ≤18.5, ]18.5–22], ]22–25], ]25–30], >30 kg/m<sup>2</sup>), and continual use of oral contraceptives or progestogens (as a time-dependent variable).

#### *Risk of onset of menopausal symptoms according to age at menopause in different time periods of menopausal transition*

Finally, we assessed whether, in the different time periods of menopausal transition (natural or artificial), the risk of onset of menopausal symptoms varied according to age at menopause (Fig. 1, for natural menopause). More than one year before natural menopause, the risk of onset of menopausal symptoms increased with increasing age at menopause ( $p$  for trend = 0.0003 in the 3–5-year period before menopause and  $p$  for trend < 0.0001 in the 1–3-year period before menopause). At other periods, the risk of onset of menopausal symptoms decreased with increasing age at natural menopause ( $p$  for trend = 0.0002 in the year before menopause,  $p$  for trend < 0.0001 in the year, 1–3 years, and 3–5 years after menopause). Results pertaining to artificial menopause were similar: in the year following menopause, the risk of onset of menopausal symptoms decreased with increasing age at menopause (HR = 1.45, 95% CI: 1.11, 1.88, HR= 1.14, 95% CI: 0.86, 1.52, and HR= 0.86, 95% CI: 0.59, 1.25, for categories of age at menopause of < 49, 49–51 and 51–53 years, respectively, compared to ≥53 years). In other categories, however, the numbers of cases were very low and risks could not be computed.

#### **Discussion**

In this large-scale longitudinal study, among women who were premenopausal (aged 40–62 years) at baseline, and who experienced menopause during the 10-year period of follow-up, we found that the risk of onset of menopausal symptoms reached a peak during the two years surrounding natural menopause. We also found that the risk of onset of menopausal symptoms in the year following menopause was higher in women who had had an artificial menopause than in women having undergone natural menopause. In other periods, the risks did not differ significantly according to type of menopause. We further observed that those who experienced their first menopausal symptoms in the 1–5-year period following menopause were more likely to have reached their menopause before 51 years. Oppositely, those who experienced their first menopausal symptoms in the 1–5-year period prior to menopause were more likely to reach their menopause at 51 years or later.

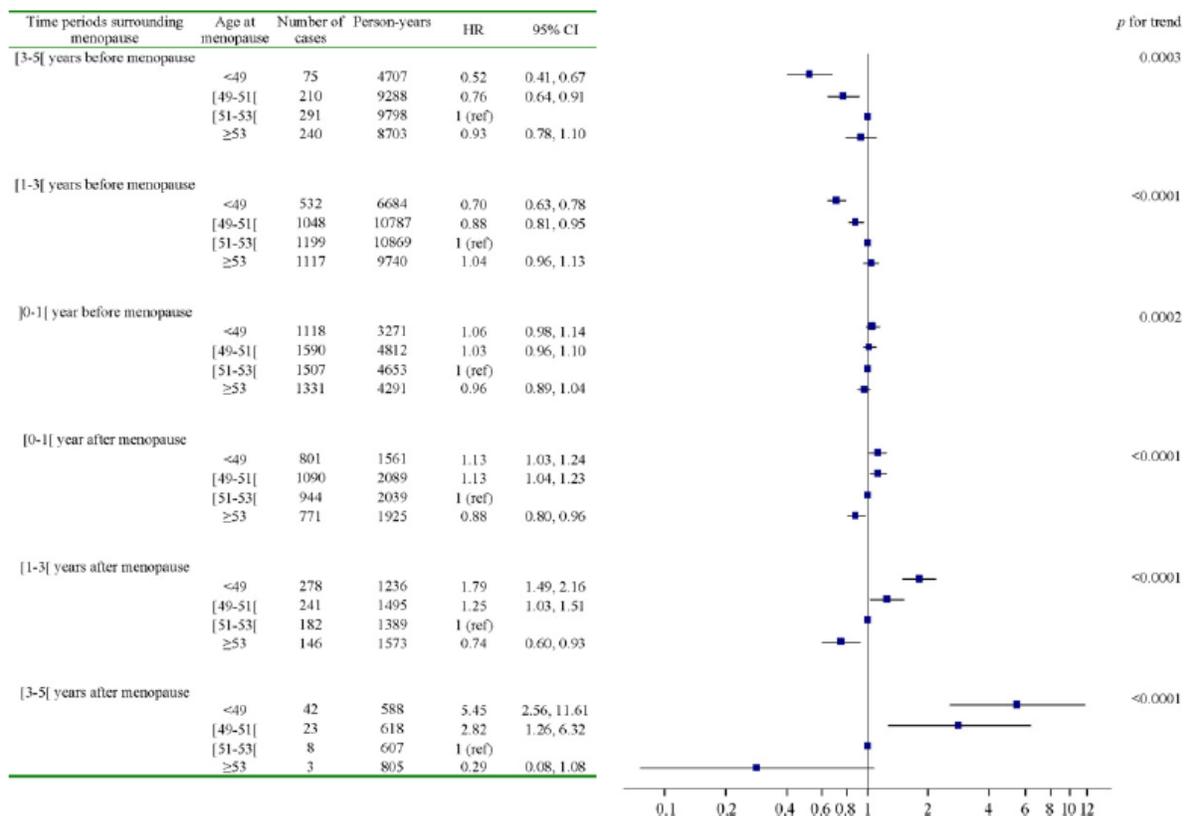


Fig. 1. Hazard ratios (HR)\* and 95% confidence intervals (CI) of onset of menopausal symptoms according to age at menopause in different time periods surrounding natural menopause, E3N, French cohort, 1990–2000.

(\*) Cox models with delay at menopause as the time scale, further adjusted for years of schooling (<12, 12–14, ≥15), alcohol consumption (quartiles, as reported in the dietary questionnaire in 1993), energy intake (<1800, 1800–2500, >2500 kcal/day as reported in the dietary questionnaire in 1993), number of children (0, 1, 2, ≥3), age at menarche (<12, 12, 13, 14, >14 years), physical activity (quartiles), usual (i.e. excluding perimenopause and periods of oral contraceptive use) duration of menstrual cycles (<25, 25–31, >31 days, irregular), smoking status (as a time-dependent variable: current, past, never), body mass index (as a time-dependent variable: ≤18.5, ]18.5–22], ]22–25], ]25–30], >30 kg/m<sup>2</sup>), and continual use of oral contraceptives or progestogens (as a time-dependent variable).

By definition, artificial menopause occurs earlier than natural menopause and leads to a sudden drop in hormone production [24]. In a recent study, fast change in estradiol slope was found associated with more severe menopausal symptoms [25]. This might explain the higher risk of onset of menopausal symptoms during the year following artificial compared to natural menopause and the higher risk of onset of menopausal symptoms when artificial menopause was experienced at a younger age.

The influence of age at menopause upon the occurrence of menopausal symptoms has already been studied: some studies showed that an age at menopause over 53 years was associated with a decrease in the risk of occurrence of hot flushes [14,15] or vaginal dryness [14], concordant with our results. Women who experienced a late menopause have been shown to have lower levels of estradiol and higher levels of follicle-stimulating hormone (FSH) in the period preceding menopause than women who reached menopause earlier [26]. High levels of FSH [7,27] or drop of estradiol [25] have been shown associated with the onset and the severity of menopausal symptoms. This is concordant with the different risk patterns observed according to age at menopause, and with the more frequent onset of menopausal symptoms in the years preceding menopause in women with menopause at 51 years or later.

Our study has several strengths. The size of our cohort allowed us to analyze specifically women who experienced menopause during follow-up, resulting in a restriction of our population, but diminishing the

potential for a recall bias without creating any selection bias, and concentrating our analysis on critical periods. Most previous studies focused on the prevalence of menopausal symptoms [2–6,8,9,12], which reflects both their onset and their duration in an indistinguishable manner. Moreover, previous studies on menopausal symptoms either included or excluded women on HRT [3,7]. We preferred to censor observations when HRT was initiated before onset of menopausal symptoms and to compute separate estimates in women with natural and artificial menopause, in order to provide valuable information on the natural history of menopausal symptoms. Finally, potential confounders [2,3,6,14–17,19] in the association between onset of menopausal symptoms and age at menopause were carefully adjusted for, and tests for interaction with adjustment factors were not significant. HR estimates were computed when possible from models which included age as the time scale, so as to compare risks of symptoms not exclusively related to the ageing process. However, the different associations between age at menopause and onset of menopausal symptoms during the periods surrounding menopause (shown in Fig. 1) could not be adjusted for the effects of aging, as the interval from (or to) menopause, age at menopause and age are linearly linked; we were therefore unable to separate the effect of each of these variables.

The major limitation of our study pertained to the absence of information on the type of menopausal symptoms. In our study, the term “menopausal symptoms” encompassed any symptom a woman perceived as being related to menopausal hormone changes, such as vasomotor symptoms, vaginal dryness, depressed mood, urinary symptoms, somatic symptoms, etc. Age at onset of menopausal symptoms was self-reported by the participants, which may have resulted in a misclassification bias. However, a validation study showed that age at menopause was rather accurately reported [18], even though in this validation study menopause may have occurred a long time before women’s self-reports of age at menopause. The present study includes only women who became menopausal during follow-up, with time intervals between onset of menopause and self-reports of age at menopause not exceeding 2–3 years (corresponding to the time between two follow-up questionnaires), thus limiting recall bias. Participants in the E3N cohort belong to a homogeneous occupational group (most are teachers or teacher’s wives with a secondary to higher educational level; 80% had 12 years or more of schooling), thus decreasing the probability that our results can be explained by educational level and other confounding factors associated with it such as smoking or alcohol consumption.

## Conclusion

In a large cohort of French women, we found that the onset of menopausal symptoms is differently distributed throughout the periods of menopausal transition depending on age at, and type of, menopause. Additional studies are needed to assess whether our results vary according to the nature of the menopausal symptoms.

## Acknowledgements

The authors are grateful to M. Fangon, L. Hoang and M. Niravong for their technical assistance; to the E3N group; and to J Bram for linguistic revision of the manuscript.

*Source of financial support:* The French League Against Cancer, 3M Company, the European Community, the Mutuelle Générale de l’Education Nationale medical insurance and the INSERM.

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