Current Smoking at Menopause Rather Than Duration Determines the Onset of Natural Menopause

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Background: Smoking has frequently been associated with early menopause. However, studies of this association have been inconclusive with regard to duration and intensity of smoking. A major problem in analyzing the effect of smoking duration on menopausal age is that both exposure and outcome are age-dependent.

Methods: We calculated age-specific rates for categories of smoking duration and subsequently computed the rate ratios for occurrence of menopause. We were thus able to model the effect of smoking duration on 2 time scales without assumptions of linearity. We used data from a Dutch population-based cohort comprising 5544 women age 49–70 years who had experienced natural menopause.

Results: The rate ratio (RR) for occurrence of menopause was increased in women who smoked in the year of menopause (RR = 1.41; 95% confidence interval = 1.32–1.50). The rate ratio of former smokers was similar to women who never smoked (0.95; 0.89–1.02). Prolonged exposure of smoking did not materially affect the risk of menopause, although the daily number of cigarettes currently smoked could increase the risk.

Conclusion: Perimenopausal smoking is apparently more important than smoking history in explaining an earlier age of onset of menopause among women who smoke.

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Numerous studies have shown that smoking affects menopausal age. Midgette and Baron[1] presented summary odds ratios based on a review of 14 studies. The general conclusion was that the risk of being postmenopausal was approximately doubled for current smokers compared with nonsmokers among women age 44 to 55 years. Depending on the biologic mechanisms at work, it might be expected that longer duration or greater intensity of smoking further reduces age of menopause. Studies have been inconclusive about dose, whereas duration has generally not been studied.[2–10] To determine the effect of smoking duration requires a method that considers the number of years smoked as a time-dependent covariate. When comparing the smoking histories of women with an early and late menopause, the probability of a longer duration of smoking for women with a later menopause is higher simply because they are older. Accordingly, even if there is no relation between smoking duration and age of menopause, a positive association would be found because both variables are time-dependent.

This study assesses the effect of smoking duration and intensity on age at menopause correcting for the chronologic age-dependency of the variables concerned.

METHODS

Data

We used data from the Prospect-EPIC cohort, Utrecht, The Netherlands.[11] Briefly, the study is a population-based cohort of 17,357 women, age 49–70 years at enrollment (1993–1997), who were recruited among participants of a breast cancer screening program.

At baseline, all participants filled out detailed questionnaires on usual diet, reproductive and medical history, and other risk factors for cancer. They underwent a brief medical examination and a blood sample was drawn. All women gave informed consent to use their data for scientific research. The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the study.

Natural menopause was defined as proposed by the World Health Organization[12] as at least 12 consecutive

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months of amenorrhea not resulting from surgery or other obvious cause. We excluded women from the study population when age at natural menopause could not be determined as a result of oral contraceptive use, hormone replacement therapy, uterus extirpation, or bilateral oophorectomy (n = 6174). Also, women who were premenopausal at time of recruitment were excluded (n = 1757) as were postmenopausal women for whom it was uncertain whether they had experienced natural menopause (n = 433). Finally, we excluded women for whom menopausal status was unknown because of missing data on either hormone use or operations or who did not fulfill the criteria of 12 months of amenorrhea (n = 2582). This left 6411 women with natural menopause.

The women were asked about current or past smoking at enrollment; the age of starting to smoke; the age of ceasing to smoke; whether there were years when they did not smoke and the duration of the stopping period; and the number of cigarettes they smoked daily at the ages of 20, 30, 40, 50, and at study entry (49–70 years). From this information we were able to assess smoking status at the age when menopause was reached and to calculate the duration of smoking up to the time of menopause. Because we had no information on the age at which interruptions occurred in a woman's smoking behavior, we excluded 867 smokers who had stopped smoking for more than a year, leaving 5544 postmenopausal women eligible for the analyses.

Other determinants that previously have been associated with both menopausal age and smoking are body mass index, parity, and socioeconomic class; these should therefore be considered as confounders.[4,13–22] Unilateral oophorectomy can be a determinant of menopausal age[23]; therefore, we checked whether these operations were equally distributed among the smoking classes. Body mass index was only assessed postmenopausally at enrollment of the study. Educational level was used as a measure of socioeconomic status. In The Netherlands, the majority of women in this generation were not educated or gainfully employed to their capacity but usually stayed home to take care of the household and children. Among married women, the educational attainment of the husband is considered a better indicator for socioeconomic status of the household to which a woman belongs,[24] and adjustments were made for the educational level of the husbands of married women.

Data Analysis

For each individual, we created new records for each follow-up year from the age of 30 onward to the age at reaching menopause, resulting in a data expansion from 5544 to 108,543 records.

For each woman, the cumulative number of years smoked and menopausal status was assessed for each year of age after age 30. Information before age 30 was summed in a single record. Thus, for each woman, the first record contained information on the number of years smoked until she reached 30 years of age and whether she reached menopause by age 30. The second record is summed from the smoking duration until age 31 years and also whether natural menopause has occurred, and so on. Next, we grouped age and the number of years smoked into categories of 5 years. Thus, individual women contribute woman-years to multiple age and smoking duration categories.

The age-specific incidence rates of menopause per 1000 woman-years were calculated for the separate groups of smoking duration. We calculated these rates by dividing the number of events (ie, occurrence of menopause) in each cell by the woman-years in the same cell. Age-adjusted rate ratios, relative risks (RR), and 95% confidence intervals (CI) were computed for smoking duration categories compared with the categories of zero years of smoking. This category includes woman-years of never-smokers, as well as of women who started smoking after 30 years of age. Approximately 6% of all smokers started smoking after 30 years of age. A rate ratio greater than one indicates a higher risk of reaching menopause at a given age (younger age at menopause), whereas rate ratios less than one indicate an older age at menopause.

We defined current smokers as women who smoked in the year of menopause and former smokers as women who smoked at least 1 year and did not smoke in the year of menopause. A stratified analysis made it possible to evaluate the separate effects of current and former smoking.

To study whether women who had been excluded from the analyses differed from those included, we compared smoking duration and menopausal characteristics between the 2 groups. Since excluded women did not reach a natural menopausal age, we calculated duration of smoking until 50 years for all women (excluded and included). Stratification by smoking status at menopause (ie, current and former smokers) is therefore not possible. The mean (± standard deviation) duration of smoking of the women included was equal to the mean for the excluded women (23.7 ± 10.0 years vs. 23.8 ± 10.1 years). The classification into categories of smoking duration did not differ for the various groups of excluded women compared with those remaining in the analysis.

In addition to duration, we also analyzed effects of dose in a similar way. To compute the number of daily cigarettes smoked for women age 30–39 years, we used the number of cigarettes smoked at age 30; for age 40–49, we used the number of cigarettes smoked at age 40, and so on. The number of cigarettes smoked daily was categorized and age-adjusted rate ratios of reaching menopause were calculated.

Educational level, parity, and body mass index (BMI = kg/m^2) were considered as confounders in all analyses.

All analyses were performed using Stata 7.0 (Stata Corp., College Station, TX) with the application effmenu by

M. Hills and D. Clayton, available at http://www-gene.cimr.cam.ac.uk/clayton/software/.

RESULTS

Table 1 summarizes the smoking habits of all women in the present analysis. On average, women of a later year of birth started smoking at earlier ages and smoked more cigarettes. Because inclusion in the study was age-dependent (49–70 years), women with later menopausal ages were underrepresented among younger women. Thus, the mean age at menopause was lower in women from later birth years because not everyone had yet reached menopause.

Of the 5544 women, 2514 reported having ever smoked before reaching menopause; among these ever-smokers, 1092 (43%) had stopped smoking before menopause, whereas the remainder had smoked until at least their last menstruation. The median age of smoking cessation before menopause was 36 years with a range of 15 to 59 years. Table 2 shows characteristics of the study population on duration of smoking and possible confounders according to the smoking status at the time of menopause.

Appendix 1 (available with the electronic version of this article) shows the number and rates of women reaching menopause according to age and smoking duration categories. We estimated the overall association of smoking with age of menopause, independent of either duration or dose and relative to never-smokers by means of a rate ratio (RR). The rate ratio was 1.41 (95% CI = 1.32–1.50) among current smokers and among former smokers of 0.95 (0.89–1.02).

Age-adjusted rate ratios of menopause for smoking duration categories compared with never-smokers are presented in Table 3. Because of the small number of former smokers who had smoked more than 25 years, we combined the categories of duration of smoking from 25 to 40 years' duration. When stratified for smoking status at age at menopause (current and former smokers), we observed an effect of smoking only among current smokers at menopausal age; this effect was independent of the number of years smoked. Except for the longest duration category, the rate ratios did not substantially differ among categories. We did not observe an effect of smoking duration in former smokers; their risk was equal to the risk of never-smokers. So, among both

TABLE 1. Smoking Characteristics of Women, Age 49–70 Years, by Year of Birth

	1924–1929 (n = 1159)	1930–1934 (n = 1496)	1935–1939 (n = 1635)	1940–1944 (n = 1033)	1945–1947 (n = 221)
Smoking status; %					
Never smoker	63	57	54	48	38
Smoker until menopausal age	24	25	24	30	32
Former smoker	14	19	22	22	30
Age when started smoking; mean ± SD	21.9 ± 7.9	20.8 ± 7.0	19.7 ± 5.6	18.9 ± 5.2	17.9 ± 4.1
No. of cigarettes/d; mean ± SD	9.3 ± 6.6	9.6 ± 7.0	10.2 ± 7.3	11.9 ± 7.5	12.9 ± 8.5
Age at natural menopause; mean ± SD	50.1 ± 4.5	50.3 ± 4.2	50.0 ± 4.0	48.1 ± 3.8	45.9 ± 3.6

TABLE 2. Characteristics According to the Smoking Status at Menopausal Age

	Smoking Status		
	Never (n = 3030)	Current (n = 1422)	Former (n = 1092)
Age at menopause (yrs); median (range)	50 (16–60)	49 (20–58)	50 (30–64)
Duration of smoking until menopause (yrs); median (range)	0	31 (1–53)	17 (1–43)
Any live born children, %	86	83	83
Educational level, %			
Primary and intermediate education, general and vocational	71	73	57
Secondary education, general and vocational	21	20	30
Academic education	8	7	13
Women with unilateral ovariectomy; no. (%)	100 (3.3)	47 (3.3)	42 (3.8)
Body mass index*; median (range)	26 (16–52)	25 (16–48)	25 (17–50)

*Measured postmenopausally at enrollment into study.

TABLE 3. Age-adjusted Rate Ratios for Occurrence of Menopause According to Duration of Smoking

Duration of Smoking (yrs)	All Smokers RR (95% CI)	Current Smokers RR (95% CI)	Former Smokers RR (95% CI)
0*	1.0	1.0	1.0
1–4	1.14 (0.92–1.40)	1.30 (0.85–2.00)	1.10 (0.87–1.39)
5–10	1.04 (0.89–1.20)	0.93 (0.61–1.43)	1.05 (0.90–1.23)
10–15	1.04 (0.92–1.18)	1.34 (1.01–1.77)	0.99 (0.81–1.13)
15–20	1.09 (0.97–1.23)	1.32 (1.07–1.63)	1.02 (0.89–1.17)
20–25	1.04 (0.93–1.15)	1.29 (1.10–1.52)	0.89 (0.78–1.03)
>25	1.30 (1.22–1.39)	1.48 (1.38–1.59)	0.79 (0.69–0.91)

*Reference category.

current and former smokers, no effect of duration of smoking was found; the rate ratios reflect the overall effect of smoking in both groups.

Adjustment for educational level, parity, and body mass index did not change the rate ratios; therefore, we present only the crude estimates.

To elaborate further on the absence of an effect for former smokers, we investigated whether the time since quitting smoking modified the association between smoking and reaching menopause. Considering current smoking as the reference group, the rate ratios of the categories of time since smoking cessation of less than 5 years, 5 to 10 years, and over 10 years were 0.75 (95% CI = 0.64–0.87), 0.78 (0.67–0.90), and 0.63 (0.57–0.69), respectively. For never-smokers, the rate ratio was 0.71 (0.67–0.76). Thus, the risk for former smokers is comparable to never-smokers irrespective of how recently the smokers had stopped smoking. Among current smokers, the effect seemed stronger with increasing amounts of smoking (Table 4). The test for linear trend had a P value of <0.0001.

DISCUSSION

Our data confirm that smoking lowers menopausal age. However, the reduction in menopausal age appears to be independent of smoking duration. For each age category, the incidence rates of menopause were higher in the smokers compared with nonsmokers, implying that smoking exerts its influence on the whole distribution of menopausal age. Thus, smoking is not a risk factor for early menopause only as some case-control studies have suggested.[14,25]

TABLE 4. Age-adjusted Rate Ratios for Occurrence of Menopause According to Daily Number of Cigarettes, Among Current Smokers

Daily No. of Cigarettes	No. of Woman-years	RR (95% CI)
1–9*	8,236	1.0
10–19	8,742	1.04 (0.91–1.10)
20–29	5,781	1.16 (1.02–1.34)
30–39	427	1.24 (0.89–1.74)
>40	194	1.02 (0.70–1.66)

*Reference category.

However, an effect of reducing menopausal age was not present in former smokers. This suggests that smoking cigarettes could have an effect only around the time of menopause itself. Furthermore, the number of cigarettes smoked in this transition period could be important because the rate ratios slightly increased with daily number of cigarettes smoked.

Because menopause is a process rather than an abrupt event, we repeated the analyses defining current and former smokers at 5 years instead of 1 year before menopause. The estimates of the effect of duration of smoking and the overall effect of smoking were similar for both definitions; the RR of the overall effect for current smokers was 1.36 (95% CI = 1.28–1.45) and for former smokers it was 0.93 (0.86–1.00). This similarity is not unexpected because the majority of women who reported to have smoked previously had stopped smoking before the perimenopausal period.

Paradoxically, some studies have reported that former smokers reach menopause at a later age than never-smokers.[1,2,10,22,26] Although most authors have considered this to be caused by misclassification of smoking status, an alternative explanation could be that smoking for awhile and subsequently quitting will inevitably lead to selection of an older group of women who are classified as former smokers. The probability of being a former rather than a current or never-smoker is increased with age and should be treated accordingly. However, even our analysis cannot entirely exclude this possibility, which could explain why the rates of former smokers in the long-duration categories tended to decrease.

We were able to assess smoking status at menopausal age. Other studies have also found an association between smoking and younger menopausal age in current smokers, but

in many studies, smoking status was established at study recruitment and did not necessarily reflect smoking status at menopausal age.[2–4,14,16] As a consequence, for some women, "current smoking" refers to premenopausal smoking and for others either peri- or postmenopausally. Even in prospective studies, smoking status is generally measured at study recruitment, resulting in smoking status being measured at a varying number of years before menopause.[27,28] Various smoking definitions among studies limits the comparability of findings on menopause associations leading to conflicting or inconclusive results.

Adjustments for potential confounding factors did not change the rate ratios by more than 3%. One limitation in our data was that body mass index was not measured premenopausally and therefore residual confounding is possible. Unilateral oophorectomy has been reported to be a strong determinant of menopausal age,[23] but because operations were equally distributed among smokers and nonsmokers, this has not confounded the results.

A potential problem in a study involving subjects of various ages could be the presence of a cohort effect. Table 2 shows that women from later birth years have higher smoking rates and lower mean ages at menopause. This relation could be caused by selective inclusion of women with relatively early menopauses as a result of incomplete follow up. In our approach, we avoided this bias by using age-specific strata. Although the cohort effect within each age-stratum should be negligible, we checked this by adjusting for birth year; this did not change the rate ratios.

Because menopausal status is measured retrospectively by questionnaire, validity and reproducibility is not 100%. However, these aspects have been addressed previously in a similar cohort.[29] The number of years since menopause decreases the validity of reporting menopausal age; the percentage of women reporting their true age at menopause was higher for more recent menopause. Both under- and overestimations were more common when more time had passed since menopause. The mean age at enrollment in the present study was 60 years, with a mean time since menopause of 10 years. If we restricted the analyses to women with no more than 5 years since menopause (n = 1491), the effect of smoking was similar; for current smokers the RR was 1.43 (95% CI = 1.26–1.60) and for former smokers it was 1.04 (0.92–1.17). Although the confidence intervals become broader because of the smaller number of women included, neither current or former smokers showed an effect of duration of smoking. If misclassification resulting from recall had occurred, then we expect that this would result in an underestimation of the effect. However, even in women with more than 5 years since menopause, we observed similar estimates.

Several biologic pathways explaining the influence of cigarette smoke on menopausal age have been suggested in the literature. One mechanism has been studied in both in vivo and in vitro mouse models carrying various genetic constructs.[30] Polycyclic aromatic hydrocarbons in cigarettes activate the aromatic hydrocarbon receptor that in turn induces the expression of the BAX apoptosis-promoting gene in oocytes and leads to an increased rate of oocyte apoptosis. If a similar induction of oocyte apoptosis by tobacco smoke exists in humans, it might be anticipated that a reduction in age of menopause would result from smoking over a wide period of time before menopause. However, this possibility is not supported by our study. Our data do not exclude an additional effect of smoking duration in the categories of 25 years or more.

A second mechanism concerns a reduced quality of developing follicles. It has been found that smokers have a lower urinary excretion of estrogen during the luteal phase, probably reflecting a lower estrogen production,[31] which could be the result of inhibition of granulosa cell aromatase.[32] Furthermore, smoking has been found to induce a shift toward a less active estrogen.[33] Thus, smoking could operate through several mechanisms that lower the estrogen level to a point where endometrial growth is no longer supported.[25] One might expect that the estrogen reduction as a result of smoking is critical only in the transition period, just before menopause, because it amplifies the effect of already decreasing hormone levels by normal ovarian aging. This agrees with a shortening of the perimenopause period observed in smokers as reported previously.[34] Therefore, we hypothesize that the onset of menopause depends not on the size of the follicle pool, but rather on the capacity to produce enough estrogens of the remaining follicles.

The relevance of an appropriate time-dependent analysis is not limited to smoking duration and age of menopause. In recent years, the search for determinants of menopausal age has frequently included age-dependent determinants such as pack-years of smoking, number of children, and number of years of oral contraceptive use. These parameters require an analysis on 2 time scales. Calculation of age-specific rates allows the study of associations in subjects of different ages and with different duration periods of exposure. The commonly used Cox regression analysis does not easily allow examination of rates, but only rate ratios. Such analysis involves assumptions that are difficult to check, particularly when modeling on 2 time scales such as age and years smoked. Although one time scale can be directly incorporated into the Cox model, the other must be modeled as a smooth linear function. It is important that the popular regression methods are not used without first checking the linear equivalence of all time scales.

Cramer et al.[25] studied the duration of smoking in both a cross-sectional and a case-control study design. In their case-control study, they found an effect only in smokers who had smoked for more than 20 years. In their cross-sectional study, analyzed by Cox regression, they showed a relation

with duration of smoking. However, both analyses were performed without separating former from current smokers at the time of menopause. These findings are not necessarily in conflict with ours, because the increased hazard ratios observed in their study might reflect a greater proportion of current smokers among those women with a longer smoking history. The strength of the present study lies in stratification by smoking status, which disentangles the effect of current smoking and possible effects of smoking duration.

In conclusion, smoking does not appear to reduce age at menopause by long-term exposure. Only women who are smoking at the age of menopause exhibit a reduction in menopausal age, which is largely independent of smoking duration.

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