



Original investigation

Smoking Across the Menopausal Transition in a 10-Year Longitudinal Sample: The Role of Sex Hormones and Depressive Symptoms

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Abstract

Introduction: Current cigarette smoking rates among older women remain problematic, especially given that this population experiences increased smoking-related health consequences. Despite these increased health concerns, little research to date has explored smoking patterns across the menopausal transition (pre-, early-peri-, late-peri-, and postmenopausal) or the effect of unique factors such as sex hormones and depression during this transition.

Methods: This study used 10 yearly waves of data from the Study of Women's Health Across the Nation, a longitudinal dataset. Data included 1397 women endorsing ever smoking regularly at baseline. Random-effects logistic regression models were used to examine smoking transitions.

Results: Although there were no associations between menopausal transition stage and smoking behavior, increased estradiol was associated with an increased likelihood of quitting regular smoking (eg, transitioning from regular smoking to non-regular or no smoking; odds ratio [OR] = 1.28), whereas increased testosterone was associated with an increased likelihood of relapsing to regular smoking (eg, transitioning from former or nonregular smoking to regular smoking OR = 2.56). Depression was associated with increased likelihood of continued smoking (OR = 0.97) and relapse (OR = 1.03).

Conclusions: The results emphasize the need to develop interventions to target initiated or continued smoking among women across the menopausal transition and specifically highlight the importance of developing treatments that target depressive symptoms in this population. In addition, although singular hormone measures were associated with smoking behavior, there is a need for future study of dynamic changes in hormones, as well as the impact of progesterone on smoking behaviors across the menopausal transition.

Implications: To date, no studies have examined smoking behaviors across the menopausal transition. In this study, although menopausal transition status was not significantly related to transitions in smoking behavior, important relationships between sex hormones and depression were observed. Increased estradiol was associated with an increased likelihood of quitting regular smoking, whereas increased testosterone was associated with an increased likelihood of relapsing to regular smoking behavior. Higher depression scores were related to continued smoking and relapse to regular smoking behavior. These results highlight the need to develop interventions to target smoking cessation among women across the menopausal transition.

Introduction

Current cigarette smoking rates among adults in the United States have recently declined, with rates decreasing from 20.9% in 2005 to 15.5% in 2016.¹ However, smoking among older women remains relatively common; among women 45–64 years old, 16.8% report current smoking.¹ This is problematic given that cigarette smoking is the leading cause of preventable death and disease in the United States and women experience a greater negative health burden when compared to men, with a greater risk of developing various cancers and cardiovascular diseases.^{2–5} In addition, women smokers have sex-sensitive and sex-specific health risks, especially associated with menopause, including earlier menopausal transition, increased risk of osteoporosis, impaired respiratory function, and more severe menopausal symptoms.^{2,6–8} Despite these increased health risks, women overall have poorer rates of smoking cessation, indicating that increased efforts are needed to understand and improve cessation rates,⁹ specifically among older women.

One potential explanation for the observed differences in cessation rates may be the hormonal milieu. During menopause, endogenous levels of estradiol and progesterone initially fluctuate during the menopausal transition, but gradually decrease to low, stable levels in postmenopause.¹⁰ Follicular stimulating hormone (FSH) levels, typically an indicator used in categorizing menopausal stage, increase substantially over the menopausal transition and remain elevated until later in life, whereas testosterone levels remain relatively stable across the transition.^{11–13} The menopausal transition is typically divided into several stages based upon fluctuating hormone levels and menstrual cycle length. Premenopause is generally a time describing a women's reproductive years, which is often characterized by regular menses and low levels of FSH; the duration of premenopause is highly variable and may be further broken down into early, peak, and late reproductive stages.^{10,14} The menopausal transition, often called perimenopause, is divided into early- and late-perimenopause based upon acyclicity. Early-perimenopause stage criteria include variable menstrual cycle length and FSH values; however, the length of this stage is also highly variable based upon the individual. Late-perimenopause is characterized by periods of amenorrhea, lasting at least 60 days, as well as high levels of FSH (greater than 25 IU/L). Late-perimenopause typically lasts 1–3 years. Finally postmenopause follows 1 year of amenorrhea, and may be further broken down into early (variable FSH levels) and late (stabilized FSH levels) stages.^{10,14} Of note, the duration of such reproductive stages is highly variable based upon a myriad of variables, such as overall health, socioeconomic status, body mass, race, ethnicity, and genetic factors.¹⁰

Among premenopausal women, there is evidence that progesterone is generally protective against smoking-related variables (eg, decreased subjective reactivity, fewer puffs of cigarettes in laboratory settings), whereas estradiol is implicated in smoking behavior (eg, relapse, continued smoking; for review, see Wetherill et al.¹⁵). However, it is worth noting that there is mixed evidence regarding the hormonal milieu, menstrual cycle, and smoking.^{15,16} As such, some studies, including one meta-analysis, have reported greater symptoms of withdrawal and craving during the luteal phase, when progesterone levels are highest.¹⁷

Regarding testosterone, smoking is associated with higher testosterone levels; however, the specific association among women smokers remains unclear and is understudied.¹⁸ Among the few studies that have examined the role of testosterone in female smoking behavior,¹⁸ higher concentrations of testosterone have been found

in premenopausal smokers relative to former female smokers and nonsmokers.¹⁹ This pattern holds true for postmenopausal smokers, with higher levels of testosterone in current versus never smokers, which was associated with the number of cigarettes smoked per day.²⁰ In addition, high levels of testosterone were also observed among the postmenopausal former smokers included in one population-cohort study.²⁰ Given the declining levels of endogenous estradiol and progesterone, as well as the stable levels of testosterone, postmenopause may be an advantageous time to make a cessation attempt. However, to date the majority of the literature has focused on the impact of sex hormones and smoking behavior among premenopausal women.¹⁷ In fact, little information is available regarding the impact of these endogenous hormones and their fluctuations on smoking cessation attempts during or after the menopausal transition.⁷

An additional factor that may explain changes in smoking behavior among older women is negative affect, specifically depressive symptoms. Women are at an increased risk of developing depressive symptoms during the menopausal transition, with a recent study showing that 31% experienced a period of persistent or recurrent depression, and 9% endorsed a single major depressive episode, across a 13-year period during the menopausal transition.^{21,22} Such associations between the menopausal transition and depressive symptoms, may be associated with the fluctuating hormonal milieu across the transition.^{7,22} This likely has a meaningful impact on female smokers, as it is well established that negative affect impedes smoking cessation attempts among smokers.^{23–25} However, little information is known regarding how depressive symptomatology affects smoking behavior across the menopausal transition.

The current scant literature regarding smoking behaviors in older women leaves several important gaps to address in order to improve cessation outcomes in this population. For instance, to the best of our knowledge, there are no studies examining smoking outcomes across the menopausal transition (pre-, early-peri-, late-peri-, and postmenopausal stages) and the impact of endogenous sex hormones and depression on such outcomes. In addition, there is a need to focus on long-term smoking cessation outcomes, as no study has examined treatment outcomes beyond a 1-year follow-up in postmenopausal women.²⁵ This information may provide necessary insights to help develop targeted interventions for cessation among women during and after the menopausal transition.

This study sought to investigate the effect of transitions across menopausal status (pre-, early-peri-, late-peri-, and postmenopausal stages) on the transition from regular smoking to nonregular or no smoking (ie, quitting regular smoking behavior) as well as the reverse transition from nonregular or no smoking, among those endorsing ever smoking to regular smoking (ie, relapse to regular smoking behavior). In addition, we analyzed the impact of sex hormones, specifically, estradiol and testosterone, as well as depressive symptoms on these changes, while accounting for age.

This study used data from the Study of Women's Health Across the Nation (SWAN). SWAN is a longitudinal, epidemiological study designed to capture the relevant biopsychosocial changes that affect women's health across the menopausal transition.²⁶ This dataset allowed investigation of the effects of menopausal status and endogenous sex hormones, as well as depression, on smoking. It was hypothesized that late-perimenopausal and postmenopausal status would be associated with an increased likelihood of quitting regular smoking in women followed across the transition and decreased likelihood of women relapsing to regularly smoking. It was hypothesized that increased levels of estradiol and testosterone would be associated

with a decreased likelihood of quitting regular smoking and an increased likelihood of relapsing to regular smoking. In addition, it was hypothesized that higher scores of depressive symptoms would be associated with a decreased likelihood of quitting regular smoking, as well as an increased likelihood of relapsing to regular smoking.

Methods

Data Source

The data used in this study are drawn from the publicly available SWAN datasets.²⁶ The study enrolled 3302 participants from seven research centers across the United States between 1996 and 1997. SWAN enrolled women who were between 42–52 years old, reported being pre- or early-perimenopausal (defined as reporting a menstrual period within the past 3 months), did not take hormone medications in past 3 months and denied a total hysterectomy (participants reported an intact uterus and at least one ovary). These participants were then followed annually over 10 years following the baseline visit with in-person examinations, which included biological measures (eg, height, weight, blood draws), as well as and surveys assessing for various physical, biological, psychological, and social changes. Additional information regarding the SWAN data and the specific variables it includes is available elsewhere.²⁶

Data Analysis

Data were analyzed using Stata Statistical Software 16.1 (2016; StataCorp, College Station, TX). Annual datasets were merged, and variables were matched based upon a source-identification variable.

Menopausal status stage was coded each year during annual surveys.²⁶ Women were identified as *premenopausal* if they reported menses within the past 3 months with no change in menstruation patterns (eg, no changes in regularity or menses occurring further or closer than previous menses). They were classified as *early-perimenopausal* if they experienced menses within the past 3 months, but identified decreased predictability between menses (eg, changes in menses being further or closer apart; changes in variability or regularity of menses). *Late-perimenopausal* women were classified as those who had reported no menses within the past 3–11 months. Finally, women reporting no menses for the past year were identified as *postmenopausal*.

Once categorized, women were not permitted to be categorized “backwards” in future visits.²⁶ In the SWAN dataset, women who reported taking hormonal therapies who had a hysterectomy and/or ovaries removed were classified as “unknown due to [hormonal therapy] use,” or “unknown due to hysterectomy,” respectively.²⁶ Accordingly, these women were not included in analyses for the years their menopausal status was marked “unknown.” In addition, given the scope of this study, women who were currently pregnant or breastfeeding were classified as such²⁶ and were excluded from the present analyses for the years they were pregnant/breastfeeding. It is important to note that the menopausal status definitions used in the SWAN study were based upon menopausal status definitions that were included in the Massachusetts Women’s Health Study^{27,28}; FSH levels were not used to categorize stages of the transitions for participants.

This study included only participants who transitioned to postmenopausal status during the 10-year period. Smokers were identified from baseline data by responding yes to a query about smoking behavior at baseline (*Have you ever smoked cigarettes regularly?*; response, yes or no). Transitions in smoking behavior were derived from an annual assessment of smoking behavior (*Do you smoke regularly since last visit?*; response, yes or no), beginning at

visit 1. Data were not censored at quitting and/or relapse to regular smoking behavior, in order to best capture subsequent transitions (eg, if a participant relapsed, then, stopped smoking regularly, then relapsed to regular smoking again, both instances were counted in the analyses).

Random-effects logistic regression models with robust standard errors were calculated using the `xtlogit` command in Stata: the association between menopausal status and transition from regularly smoking to nonregular or no smoking (eg, quitting regular smoking) between any waves of data collection, as well as the association between menopausal status and transition from nonregular or no smoking to regularly smoking between any waves of data collection, among those identified as “*ever smokers*” (eg, relapse to regular smoking). Baseline age, age of postmenopausal status, and length of transition from early-peri- to postmenopausal status were included in all models. Annual measures of hormonal assays, including estradiol and testosterone, were included in the second and third models. Estradiol and testosterone results did not have normal distributions, and thus natural log-transformed values were used. This strategy has been used in other analyses of SWAN hormonal data (eg, Lasley et al.²⁹ and Luetters et al.³⁰). Of note, FSH was not included in current analyses, due to multicollinearity with the menopausal transition variable. Depression symptoms were also evaluated annually, with the Center for Epidemiological Studies Depression Scale (CES-D),³¹ and were included in the third model.

Results

Baseline data identified 1397 women as being ever regular smokers. Of the identified baseline, ever regular smokers, the majority were White, non-Hispanic (54.40%; Black and/or African American, 30.60%; Hispanic, 6.70%; Asian and/or Asian American, 8.30%). Mean age at baseline was 45.84 years (SD = 2.67 years).

Transition From Smoking Regularly to Quitting Regular Smoking

There were no significant associations between menopausal status and the transition from smoking regularly to not regularly smoking or not smoking. However, increased estradiol levels were associated with an increased likelihood of quitting regular smoking. Testosterone levels were not significantly related to the transition to quitting regular smoking. In addition, increased depressive symptoms (measured via CES-D) decreased one’s likelihood of quitting regular smoking. See [Table 1](#) for complete results.

Transition from Former Smoker or Not Smoking Regularly to Smoking Regularly

Again, no significant association between menopausal status and the transition from nonregular or no smoking, among former “*ever smokers*,” to regular smoking (eg, relapse) were observed. Similarly, estradiol levels were not significantly related to transition to relapse to regular smoking. However, increased levels of testosterone and depression (measured via CES-D) were associated with an increased likelihood of relapsing. See [Table 2](#) for complete results.

Discussion

Given the scant literature investigating the menopausal transition and smoking outcomes to date,⁷ this study sought to explore the

Table 1. Association Between Menstrual Status and Transition From Regular Smoking to Quitting

	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Menopausal transition status						
Premenopausal	Reference		Reference		Reference	
Early-perimenopausal	2.29 (0.56 to 9.46)	.251	1.70 (0.29 to 9.89)	.553	1.92 (0.29 to 12.84)	.501
Late-perimenopausal	1.32 (0.13 to 13.49)	.817	0.91 (0.06 to 13.85)	.945	1.09 (0.06 to 21.00)	.952
Postmenopausal	2.46 (0.31 to 19.87)	.397	1.60 (0.11 to 22.77)	.728	1.85 (0.11 to 30.29)	.665
Age (years) ^a	0.95 (0.69 to 1.30)	.735	1.06 (0.74 to 1.54)	.740	1.06 (0.69 to 1.62)	.796
Age of postmenopause (years)	1.14 (0.84 to 1.56)	.403	1.07 (0.74 to 1.55)	.733	1.08 (0.69 to 1.62)	.745
Length of transition (years) ^b	1.00 (0.76 to 1.31)	.994	1.05 (0.76 to 1.44)	.786	1.05 (0.74 to 1.48)	.778
Estradiol (pg/mL) ^c			1.28 (1.09 to 1.51)	.003	1.28 (1.08 to 1.50)	.004
Testosterone (ng/dL) ^c			0.85 (0.56 to 1.29)	.446	0.80 (0.54 to 1.19)	.275
Depression (CES-D), total score					0.97 (0.94 to 1.00)	.022

Bold font indicates significance. CES-D = Center for Epidemiological Studies Depression Scale; CI = confidence interval; OR = odds ratio.

^aAt baseline.

^bYears from early-peri- to postmenopause.

^cNatural log-transformed hormonal assay results.

Table 2. Association Between Menstrual Status and Transition to Relapsing to Regular Smoking

	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Menopausal transition status						
Premenopausal	Reference		Reference		Reference	
Early-perimenopausal	0.83 (0.13 to 5.29)	.844	0.72 (0.11 to 4.53)	.726	0.64 (0.09 to 4.38)	.649
Late-perimenopausal	0.92 (0.19 to 4.50)	.921	0.74 (0.16 to 3.36)	.693	0.68 (0.16 to 3.12)	.622
Postmenopausal	0.71 (0.11 to 4.38)	.712	0.59 (0.08 to 4.29)	.601	0.54 (0.07 to 4.33)	.563
Age (years) ^a	0.92 (0.70 to 1.19)	.515	0.96 (0.68 to 1.34)	.797	0.99 (0.68 to 1.43)	.958
Age of postmenopause (years)	0.88 (0.70 to 1.09)	.238	0.87 (0.66 to 1.15)	.323	0.84 (0.62 to 1.43)	.256
Length of transition (years) ^b	1.16 (0.87 to 1.56)	.310	1.21 (0.82 to 1.77)	.330	1.25 (0.82 to 1.90)	.309
Estradiol (pg/mL) ^c			1.09 (0.80 to 1.48)	.578	1.11 (0.82 to 1.51)	.483
Testosterone (ng/dL) ^c			2.77 (1.48 to 5.17)	.001	2.56 (1.02 to 1.04)	.007
Depression (CES-D), total score					1.03 (1.02 to 1.04)	<.001

Bold font indicates significance. CES-D = Center for Epidemiological Studies Depression Scale; CI = confidence interval; OR = odds ratio.

^aAt baseline.

^bYears from early-peri- to postmenopause.

^cNatural log-transformed hormonal assay results.

effect of menopausal status on smoking behavior. Although our results did not demonstrate an association between the transition through menopause stages and quitting and/or relapsing of regular smoking behavior, the present results did illustrate that it is likely that other unique factors related to the menopausal transition are related to changes in smoking behavior.

One of these unique factors related to smoking outcomes across the menopausal transition is likely the hormonal milieu, given the previous evidence that endogenous sex hormone levels affect smoking cessation in premenopausal women.¹⁷ In the current investigation, testosterone was related to an increased likelihood of relapse to regular smoking, with no significant effect on the likelihood of quitting regularly smoking behaviors. This supports previous literature that both male and female smokers, relative to nonsmokers or former smokers, have higher levels of testosterone.¹⁸⁻²⁰ Thus, it is likely that smoking increased testosterone levels among those smoking regularly, although future research should explore potential casual relationships and measure serum testosterone at multiple timepoints to capture potential dynamic changes in relation to smoking behavior.

In this study, increased levels of estradiol increased the likelihood of quitting regular smoking; however, it was unrelated to relapse. This was contrary to the hypothesis that increased estradiol, which is generally associated with increased cravings, would be related to poorer smoking outcomes (ie, less likely to transition to nonregular or no smoking and more likely to relapse to regular smoking). Previous research has asserted that estrogen is related to accelerated nicotine metabolism among premenopausal women; however, "menopausal" or postmenopausal women' nicotine metabolism does not differ from that of male smokers.³² Thus, women across the menopausal transition may be less susceptible to the proposed effects of estradiol on smoking behavior.

However, additional investigation regarding ovarian hormones and smoking cessation is still warranted in this population, specifically with future studies collecting hormonal assays at multiple timepoints throughout the menopausal transition. There is emerging evidence that endogenous progesterone levels are related to smoking abstinence among premenopausal women.³³ It may be that progesterone, which decreases across the menopausal transition, also

affects transitions in smoking behaviors during the menopausal transition. Unfortunately, progesterone levels were not included in the publicly available, annual hormonal assays of the SWAN study; thus, the effect of progesterone and its metabolites (eg, allopregnanolone) on smoking transitions were unable to be explored through this dataset.²⁶ Progesterone levels may also be needed to understand estrogen's effects on smoking behavior, as previous research has shown that the ratio of progesterone to estradiol is a useful predictor of smoking behavior.¹⁶

An additional factor related to smoking outcomes among older women is depressive symptoms. Previous literature has established that negative affect and depression negatively affects smoking cessation in postmenopausal women.^{7,25} This study supported this finding in that depressive symptomatology was significantly related to a decreased likelihood of quitting regular smoking, as well as an increased likelihood of relapsing to smoking regularly. Research has found that postmenopausal women with a history of depression are less likely to quit smoking, compared to those with no history of depression.²⁵ Given the previous research and this study's results that depressive symptoms are significantly related to the increased likelihood of continued regular smoking, further study of the mechanisms underlying negative affect management and smoking during the menopausal transition are warranted in order to develop cessation interventions that target depressive symptomatology in this population.

Overall, although the present results did not demonstrate that menopausal status is associated to transitions in smoking behavior; they do illustrate that women are making transitions in smoking behavior as they age. Previous research among older smokers has shown that older smokers who are motivated to quit, have at least as high of a chance of quitting as their younger counterparts, especially when using nicotine replacement therapies.³⁴ This highlights the need to develop novel interventions to increase motivation to quit smoking and improve cessation outcomes among this population. Previous research has shown that menopausal symptom severity, including somatic menopausal symptoms (eg sweating, hot flashes, cardiac complaints), was related to increased motivation to quit smoking³⁵; thus, evaluating one's health and menopausal symptomatology may increase motivation to quit smoking among postmenopausal women.³⁵ In future work, it may be beneficial to incorporate health evaluation into motivational-based interventions with this population. In addition, addressing other potential barriers to cessation, including psychosocial stress may be advantageous. These avenues may offer important insight into the development of novel treatments for tobacco cessation for this population.

Limitations

To the best of our knowledge, this study is the first study to explore transitions in smoking behavior across the menopausal transition and investigate the impact of sex hormones. However, there are limitations that warrant mention. First, although the sample is composed of a racially and ethnically diverse sample, drawn from seven geographic locations across the United States, results may not be generalizable to women in other countries. Second, data analysis was limited to variables collected at annual assessment visits, as well as the study's inclusion and exclusion criteria (including age restrictions). As such, there is limited information to help us further characterize and understand factors related to smoking transitions. For example, more detailed questions regarding past year smoking behavior and measures of nicotine dependence were not available for

the current study. Measures of depressive symptomatology were also only obtained annually, with a measure that surveys such symptoms over the past week. Thus, this may reflect state affect, as opposed to representing affect, as well as fluctuations in mood, across the past year. Furthermore, menopausal status classification did not include a biological confirmation. Inclusion of these variables would improve future research on this topic.

In addition, sex hormone measurements were taken at only one timepoint at each annual visit and thus may not accurately represent the role of fluctuating hormones across the menopausal transition in relation to smoking. Future studies should include more comprehensive hormone assay collection. Finally, smoking behavior was self-reported and no biological measures were collected, thus smoking behavior may be subject to biased reporting. Despite these limitations, given the limited literature available on smoking across the menopausal transition, the present data are a valuable contribution to the literature. Future investigations are needed to replicate and reproduce the current results.

Conclusions

To the best of our knowledge, results from the present investigation are the first to demonstrate unique factors that affect transitions in smoking behavior among women across the menopausal transition. Estradiol levels were associated with an increased likelihood of quitting regular smoking, whereas testosterone levels were related to an increase in likelihood to relapse to regular smoking. Similar to previous research among other populations of smokers, depressive symptoms were related to a decreased likelihood to quit regular smoking, whereas such symptomatology was also related to an increase in likelihood to relapse to regular smoking among this population. These results emphasize the importance of developing interventions potentially targeting depressive symptoms to improve smoking cessation among women across the menopausal transition. Future research is needed to explore additional barriers to cessation among this population. In addition, the examination of the impact of progesterone on cessation outcomes during the menopausal transition is warranted.

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Declaration of Interests

None declared.

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