GYNECOLOGY

Early natural menopause is associated with poor lung health and increased mortality among female smokers

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BACKGROUND: Early natural menopause has been regarded as a biomarker of reproductive and somatic aging. Cigarette smoking is the most harmful factor for lung health and also an established risk factor for early menopause. Understanding the effect of early menopause on health outcomes in middle-aged and older female smokers is important to develop preventive strategies.

OBJECTIVE: This study aimed to examine the associations of early menopause with multiple lung health and aging biomarkers, lung cancer risk, and all-cause and cause-specific mortality in postmenopausal women who were moderate or heavy smokers.

STUDY DESIGN: This study was conducted on postmenopausal women with natural (n=1038) or surgical (n=628) menopause from the Pittsburgh Lung Screening Study. The Pittsburgh Lung Screening Study is a community-based research cohort of current and former smokers, screened with low-dose computed tomography and followed up for lung cancer. Early menopause was defined as occurring before 45 years of age. The analyses were stratified by menopause types because of the different biological and medical causes of natural and surgical menopause. Statistical methods included linear model, generalized linear model, linear mixed-effects model, and time-to-event analysis.

RESULTS: The average age of the 1666 female smokers was 59.4±6.7 years, with 1519 (91.2%) of the population as non-Hispanic Whites and 1064 (63.9%) of the population as current smokers at baseline. Overall, 646 (39%) women reported early menopause, including 198 (19.1%) women with natural menopause and 448 (71.3%) women with surgical menopause ($P<.001$). Demographic variables did not differ between early and nonearly menopause groups, regardless of menopause type. Significant associations were identified between early natural menopause and higher risk of wheezing (odds ratio, 1.65; $P<.01$), chronic bronchitis (odds ratio, 1.73; $P<.01$), and radiographic emphysema (odds ratio, 1.70; $P<.001$) and lower baseline lung spirometry in an obstructive pattern (−104.8 mL/s for forced expiratory volume in the first second with $P<.01$, −78.6 mL for forced vital capacity with $P=.04$, and −2.1% for forced expiratory volume in the first second—to—forced vital capacity ratio with $P=.01$). In addition, early natural menopause was associated with a more rapid decline of forced expiratory volume in the first second—to—forced vital capacity ratio (−0.16% per year; $P=.01$) and incident airway obstruction (odds ratio, 2.02; $P=.04$). Furthermore, women early natural menopause had a 40% increased risk of death ($P=.023$), which was mainly driven by respiratory diseases (hazard ratio, 2.32; $P<.001$). Mediation analyses further identified that more than 33.3% of the magnitude of the associations between early natural menopause and all-cause and respiratory mortality were explained by baseline forced expiratory volume in the first second. Additional analyses in women with natural menopause identified that the associations between continuous smoking and subsequent lung cancer risk and cancer mortality were moderated by early menopause status, and females with early natural menopause who continued smoking had the worst outcomes (hazard ratio, >4.6; $P<.001$). This study did not find associations reported above in female smokers with surgical menopause.

CONCLUSION: Early natural menopause was found to be a risk factor for malignant and nonmalignant lung diseases and mortality in middle-aged and older female smokers. These findings have strong public health relevance as preventive strategies, including smoking cessation and chest computed tomography screening, should target this population (ie, female smokers with early natural menopause) to improve their postmenopausal health and well-being.

Key words: early menopause, lung aging, lung cancer, mortality, smoker

Introduction

Natural cessation of menstruation (ie, menopause) results from the decline in estrogen levels driven by ovarian aging[1] and initiates the nonreproductive phase of a woman's life. Natural menopause commonly occurs in women between 45 and 55 years of age. The menopausal transition, during which endogenous production of estrogens is gradually taken over by the adipose tissue, lasts approximately 5 years.[2,3] Some tissues, including the lung, may contribute appreciably to local estrogen synthesis in the postmenopausal state.[4–6] Moreover, surgical interventions can cause or facilitate menopause, and patients receiving oophorectomy often need subsequent hormone therapy (HT) to cope with estrogen withdrawal symptoms.[7] Studies have identified many health conditions, such as cardiovascular diseases (CVDs) and osteoporosis, whose risk elevates dramatically in postmenopausal women, and estrogen loss has been regarded as the key cause of postmenopausal symptoms and health conditions.[8] With increasing life expectancy and greater exposure to estrogen associated with a modern reproductive pattern (ie, earlier age at menarche, delayed reproduction, and lower

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AJOG at a Glance

Why was this study conducted?

Cigarette smoking is the most harmful factor for lung health. Early natural menopause is a biomarker of reproductive and somatic aging. Understanding the effect of early menopause on health outcomes in middle-aged and older female smokers is important to develop preventive strategies.

Key findings

Early natural menopause was associated with worse lung health, accelerated lung aging, and higher all-cause and respiratory mortality. Females with early natural menopause who continued smoking had a dramatically (>4.5-fold) increased risk of lung cancer (LC) and cancer-specific mortality.

What does this add to what is known?

The effects of early menopause on lung health and aging sequela were rarely studied in female smokers. This study has provided strong evidence supporting the importance of maintaining lung health in female smokers with early natural menopause. Moreover, female smokers with early natural menopause should be targeted for smoking cessation and LC screening.

fertility),[9] it is important to delineate the effect of menopause timing and estrogen exposure on subsequent disease development, which is essential for health maintenance and disease prevention in older females.

Compromised lung health is associated with many aging-related morbidities and mortalities. Cigarette smoking remains the most common and harmful factor for impairing lung health with the attributing loss of lung function not reversible after smoking cessation. Thus, characterization of host factors that contribute to the impairment of lung health in cigarette smokers is of translational importance because it is imperative for those susceptible individuals to adopt healthier behaviors. Studies from the European Community Respiratory Health Survey identified the following:

1. The biochemically confirmed menopause transition (ie, menstruation to transition to menopause) accelerated age-related decline of forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC); however, it is unknown whether this accelerated decline pattern would remain after menopause.
2. Postmenopausal women had a higher risk of respiratory symptoms and lower FEV_1 and FVC than menstruating women.
3. The effect of menopause on lung function followed a restrictive pattern (ie, stronger effect on FVC than FEV_1).[10,11]

Those studies provided evidence supporting immediate and simultaneous effects of waning estrogen accompanying menopause transition on FEV_1 and FVC that result in an irreversible loss of lung function through the postmenopausal period. It is important to note that cigarette smoking is also the most established factor for early menopause and its intensity, duration, cumulative dose, and earlier initiation have been all associated with early menopause.[12] Thus, it is crucial to disentangle the relationship between smoking, menopause and its timing, and health effects. For example, a study on British women identified that menopause exaggerated the effect of cigarette smoking on lung function,[13] supporting a potential synergistic effect of cigarette smoking and menopause on lung function.

In line with these findings regarding menopause and lung function, early age at natural menopause was reported to be associated with a higher risk of hospitalization or death in patients with incident chronic obstructive pulmonary disease (COPD) and lower lung function in a restrictive pattern in the UK Biobank.[14] A similar pattern affecting lung function for early natural menopause was also observed in the Tasmanian Longitudinal Health Study.[15] Moreover, marked associations between early menopause and all-cause mortality were consistently reported in the literature.[16–21] In cause-specific mortality analyses, early menopause was associated with increased mortality for CVDs but reduced mortality for breast, uterine, and ovary cancers.[18,19] It is hypothesized that early menopause could be a marker of accelerated reproductive and somatic aging (eg, osteoporosis, compromised immune function, and suboptimal musculoskeletal function) that underlies the increased mortality in postmenopausal women.[17,22–25]

Given that evidence-based interventions for middle-aged and older female current and former smokers may improve morbidity and mortality, we aimed to assess (1) the associations between early menopause and lung health biomarkers, including respiratory symptoms, radiographic emphysema, bronchitis, and longitudinal spirometry; (2) the associations between early menopause and lung cancer (LC) risk and all-cause and cause-specific mortality, in 1666 postmenopausal women from the Pittsburgh Lung Screening Study (PLuSS) who were moderate to heavy smokers. We hypothesized that early menopause is associated with worse lung health outcomes and higher LC incidence and mortality in current and former smokers.

Methods

Study population

The PLuSS cohort was a community-based research cohort of current and former smokers, screened with low-dose computed tomography (CT) and followed up for LC.[26] Between 2002 and 2005, 3642 participants were enrolled in PLuSS. The eligibility criteria were age of 50 to 79 years, smoked half a pack of cigarettes per day or more for at least 25 years, smoking cessation was no more than 10 years before enrollment (if the

individual quit smoking), and no personal history of LC. During study entry, the participants completed a questionnaire, provided a blood sample, and underwent low-dose CT screening and spirometry. The participants underwent a repeat low-dose CT screening approximately 1 year later. The questionnaires covered demographics, smoking history, respiratory conditions and symptoms, comorbidities, and menstrual and reproductive history (the last 2 items are only for women). The current analysis included female PluSS participants who reported natural (n=1038) or surgical (n=628) menopause status at study entry.

Menstrual and reproductive history

Menstrual and reproductive history were collected in the baseline questionnaire through the following questions: question 27, "Are you still having menstrual periods? (1) No; (2) Yes"; question 28, "How old were you when you had your last period? (1) Less than 40 years; (2) 40 to 44 years; (3) 45 to 49 years; (4) 50 to 54 years; (5) 55 years or older"; question 29, "Did your periods stop because of natural menopause, surgery, radiation, or drug therapy? (1) Natural menopause; (2) Surgery; (3) Radiation; (4) Drug therapy"; and question 38, "Sometimes women take female hormones, such as estrogen or progesterone, around the time of menopause. Have you ever used female hormones (tablets, pills, or creams) for menopause? (1) No; (2) Yes". Early menopause was defined as age at menopause (AAM) of <45 years.

Outcomes of interest

Variables from the baseline questionnaire

Self-reported respiratory symptoms were cough, phlegm, wheezing, and dyspnea, and physician-diagnosed cardiopulmonary comorbidities were coronary heart disease or myocardial infarction, stroke, coronary artery bypass or angioplasty, and chronic bronchitis.

Radiographic emphysema score from the baseline computed tomography scan

Based on the National Emphysema Treatment Trial criteria, baseline chest CT scans (n=1606) were evaluated through visual scoring for emphysema presence and severity, with ordinal scores for no, trace, mild, moderate, and severe emphysema, the latter 4 categories roughly corresponding to emphysema affecting <10%, 10% to 25%, 25% to 50%, and >50% of the lung, respectively.[27] Because few participants (n=20) had severe emphysema, this group was combined with the moderate group for data analysis.

Spirometry and related outcomes

A total of 1666 female smokers received spirometry at baseline. Spirometry was performed following the American Thoracic Society standards. Among the 1666 study participants, 824 had ≥2 spirometry tests because of their enrollment into PLuSS-X (n=389) and the PluSS Supplemental Sample Collection (n=435). The PluSS-X protocol was implemented in 2006, and it ended in 2016; furthermore, the PluSS-X protocol enrolled 977 PluSS men and women determined to be at the highest risk of LC who underwent CT screening every other year and spirometry every year and also provided yearly blood and sputum samples (2006−2016). Individuals eligible for PLuSS-X had to satisfy at least one of the following criteria: (1) ≥2.5% 5-year cumulative LC risk (Bach model), (2) moderate or severe structural emphysema on the baseline low-dose CT, (3) moderate or severe airflow obstruction on the baseline spirometry, (3) ≥2 first-degree relatives with an LC diagnosis, and (4) moderate or high suspicion of lung nodule on both baseline and 1-year later repeated low-dose CT scan with delinquent diagnostic follow-up. The eligibility criteria for the PLuSS Supplemental Sample Collection (2011−2016) include PLuSS participant, no LC detected, not lost to follow-up (or death), and not already part of PLuSS-X. The PLuSS Supplemental Sample Collection aimed to (1) update questionnaire-based risk factor information, (2) collect and store blood, (3) collect and store sputum, (4) retest pulmonary function, (5) measure exhaled carbon monoxide, and (6) repeat a low-dose CT for LC screening among those not followed up under the PLuSS-X protocol. We analyzed the distribution of several important variables between female smokers with ≥2 spirometry (n=824) and those with 1 spirometry (n=842). The percentage of surgical menopause was 35.6% in participants with ≥2 spirometry tests vs 39.8% in those with only 1 spirometry test (P=.08). The percentage of early menopause was 38.0% in participants with ≥2 spirometry tests vs 40.0% in those with only 1 spirometry test (P=.51). No statistically significant difference was identified for baseline values of age (P=.57), smoking status (P=.66), body mass index (BMI; P=.10), and spirometry (FEV_1 [P=.78], FVC [P=.15], and FEV_1-to-FVC ratio [P=.12]) between these 2 groups. Airway obstruction was defined as an FEV_1-to-FVC ratio of <70% according to the Global Initiative for Chronic Obstructive Lung Disease.[28] Incident airway obstruction was defined as newly diagnosed airway obstruction among participants (n=485) without airway obstruction at baseline.

Lung cancer incidence and mortality

Incident LC was identified through CT screenings, National Death Index (NDI), obituary data, or self-reports from study participants or their next of kin. Pathology reports were reviewed to collect the date, stage, and histology of LC diagnosis. Mortality data were acquired from the NDI, obituary data, annual follow-up contact, and letters or calls from family members with May 2020 as the cutoff date. Death certificates were reviewed to collect dates and causes of death.

Longitudinal smoking status

Participants were followed annually to update their smoking status and cancer diagnosis with May 2020 as the last follow-up date and were classified into continuous, former, and intermittent smokers as described in the Supplemental Materials and Methods.

TABLE 1
Baseline variables and longitudinal smoking status in the Pittsburgh Lung Screening Study female smokers by menopause type and early menopause status

	Natural menopause				Surgical menopause			
Variable	Subtotal	Early	Nonearly	*P* value[a]	Subtotal	Early	Nonearly	*P* value[a]
n	1038	198	840		628	448	180	
Age (y)	59.3±6.8	59.6±7.4	59.2±6.6	.49	59.6±6.5	59.6±6.3	59.5±6.9	.76
BMI (kg/m^2)	28.2±5.8	28.2±5.9	28.2±5.7	.96	28.8±6.1	29.0±6.1	28.2±6.2	.16
BMI group				.95				.077
Normal or underweight	333 (32.1)	65 (32.8)	268 (31.9)		186 (29.6)	121 (27.0)	65 (36.1)	
Overweight	382 (36.8)	71 (35.9)	311 (37.0)		225 (35.8)	167 (37.3)	58 (32.2)	
Obesity	323 (31.1)	62 (31.3)	261 (31.1)		217 (34.6)	160 (35.7)	57 (31.7)	
Current smoker	654 (63.0)	128 (64.7)	526 (62.6)	.60	410 (65.3)	294 (65.6)	116 (64.4)	.78
Pack-years	45.6±19.5	46.2±18.3	45.5±19.8	.47	47.1±20.4	47.5±20.6	46.0±19.9	.26
Ethnicity				.037				.97
Non-Hispanic White	959 (92.4)	175 (88.4)	784 (93.3)		560 (89.2)	399 (89.1)	161 (89.4)	
African American	57 (5.5)	15 (7.6)	42 (5.0)		60 (9.6)	43 (9.6)	17 (9.4)	
Others[b]	22 (2.1)	8 (4.0)	14 (1.7)		8 (1.3)	6 (1.3)	2 (1.1)	
Ever HT	627 (60.5)	123 (62.1)	504 (60.1)	.60	501 (79.9)	355 (79.4)	146 (81.1)	.63
Emphysema score				.003				.78
None	597 (59.8)	97 (50.5)	500 (62.0)		368 (60.5)	265 (61.1)	103 (59.2)	
Trace	164 (16.4)	30 (15.6)	134 (16.6)		114 (18.8)	81 (18.7)	33 (19.0)	
Mild	136 (13.6)	36 (18.8)	100 (12.4)		82 (13.5)	55 (12.7)	27 (15.5)	
Moderate and severe	101 (10.1)	29 (15.1)	72 (8.9)		44 (7.2)	33 (7.6)	11 (6.3)	
FEV1 (L/s)	2.07±0.58	1.92±0.59	2.11±0.57	<.0001	2.00±0.55	1.99±0.55	2.03±0.55	.40
FVC (L)	2.92±0.65	2.77±0.64	2.96±0.64	.0003	2.82±0.63	2.81±0.62	2.86±0.65	.38
FEV1-to-FVC ratio (%)	70.4±11.0	68.6±12.5	70.8±10.5	.013	70.4±10.5	70.2±10.6	70.7±10.3	.61
Cancer history	110 (10.6)	19 (9.6)	91 (10.8)	.61	101 (16.1)	74 (16.5)	27 (15.0)	.64
Reproductive cancer history	10 (1.0)	3 (1.5)	7 (0.8)	.38	34 (5.4)	25 (5.6)	9 (5.0)	.77
Longitudinal smoking status				.24				.66
Continuous smoker	370 (35.7)	79 (39.9)	291 (34.6)		237 (37.7)	169 (37.7)	68 (37.8)	
Former smoker	446 (43.0)	84 (42.4)	362 (43.1)		266 (42.4)	186 (41.5)	80 (44.4)	
Intermittent smoker	222 (21.4)	35 (17.7)	187 (22.3)		125 (19.9)	93 (20.8)	32 (17.8)	

Data are presented as mean±standard deviation or number (percentage), unless otherwise indicated.

BMI, body mass index; *FEV1*, forced expiratory volume in the first second; *FVC*, forced vital capacity; *HT*, hormone therapy.

[a] The 1-way analysis of variance for continuous variables and the chi-squared test for categorical variables were used to obtain the *P* values. The Mantel-Haenszel chi-squared test was used for the BMI group and radiographic emphysema; [b] Others include Hispanic, Asian, Pacific Islander, American Indian, or Alaskan Native.

Zhai. Early menopause and lung aging in female smokers. Am J Obstet Gynecol 2022.

Statistical analysis

All analyses were performed on natural and surgical menopause separately because of different biological and medical causes of natural and surgical menopause. The variables were summarized by early menopause status using statistics based on their nature (ie, categorical vs continuous) and distribution (ie, skewed vs normal) and were compared using parametric or nonparametric methods for continuous variables and chi-squared tests for categorical variables (Table 1).

A logistic model was used to assess the associations between early menopause (early vs nonearly menopause) and HT (ever vs never) and respiratory symptoms (eg, cough, phlegm, wheeze, and dyspnea) and lung comorbidities (eg, chronic bronchitis, airway obstruction,

and emphysema score) at baseline. A linear model was used to associate early menopause and HT with spirometry at baseline. A linear mixed-effects (LME) model with a subject-specific random intercept and slope was used to assess the effect of early menopause and HT on spirometry decline by including interaction terms with time in cohort. Cox proportional-hazards models were used to assess the effect of early menopause and HT on LC risk and mortality based on all-cause, LC, all-cancer, CVD, and respiratory diseases. When assessing disease-specific mortality, death because of other or unknown causes was treated as a competing risk. Covariates adjusted in the aforementioned models included age at enrollment, ethnicity (African American and others with non-Hispanic White [NHW] as the reference), BMI group (BMI of 25−30 and BMI of ≥30 with a BMI of <25 as the reference), baseline smoking status (for baseline endpoints), longitudinal smoking status (LSS, former and intermittent smokers with continuous smokers as the reference and for long-term health outcomes), and baseline pack-years. Height was additionally adjusted in models with spirometry as an outcome. For endpoints associated with early menopause status with P values of <.05, we further assessed whether the associations with the AAM groups follow a monotonically increasing or decreasing trend. AAM was coded as 1 for AAM at >50 years, 2 for AAM at 45 to 49 years, 3 for AAM at 40 to 44 years, and 4 for AAM at <40 years and was included in the trend test modeling as a continuous variable. We further calculated the estimates and P values for individual AAM categories (ie, 45−49, 40−44, and <40 years) with AAM at >50 years as the reference to better understand the monotonically increasing or decreasing trends. We are aware of the smaller sample size for age at natural menopause at <40 years (n=41); thus, we coded the most common group, that is, AAM at >50 years (n=471), as "1" or reference group for the trend test. Because of concerns for multiple comparisons, we mainly focused on the results with P values of <.01 for early menopause and/or those with P values for trend tests of <.05. Mediation analysis was performed on the basis of an established method[29] to explore the mediational effect of baseline spirometry on associations between early menopause and mortality. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC).

Results

Study participant characteristics

The average age of the 1666 female smokers from the PLuSS cohort was 59.4±6.7 years, with 1519 (91.2%) and 117 (7.0%) of the population as NHWs and Blacks, respectively. Of note, 1064 (63.9%) of the population were current smokers with an average pack-years of 46.1±19.8 years at baseline. Overall, 646 (39%) women in the sample reported early menopause, including 198 (19.1%) women with natural menopause and 448 (71.3%) women with surgical menopause (Table 1). Women with surgical menopause had a higher rate of HT use (501 [79.9%] vs 627 [60.5%]; P<.001), a higher percentage of African Americans (60 [9.1%] vs 57 [5.2%]; P<.01), a higher personal cancer history (101 [16.1%] vs 110 [10.6%]; P<.01), and a higher reproductive cancer history (34 [5.4%] vs 10 [1.0%]; P<.001) than women with natural menopause. Comparisons between early and nonearly menopause groups did not identify any substantial differences in demographic variables (age, BMI, smoking status, and pack-years), regardless of menopause types.

Associations of early menopause with health conditions

Early menopause was associated with self-reported wheeze (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.18−2.30; P<.01), physician-diagnosed chronic bronchitis (OR, 1.73; 95% CI, 1.19−2.53; P<.01), and CVD (OR, 1.87; 95% CI, 1.13−3.11; P=.02), radiographic emphysema (OR, 1.70; 95% CI, 1.25−2.31; P<.001), and incident airway obstruction (OR, 2.02; 95% CI, 1.03−3.96; P=.04) in females with natural menopause (Table 2), but not in females with surgical menopause except for physician-diagnosed CVDs (OR, 4.03; 95% CI, 1.78−9.14; P<.001) (Supplemental Table 1). Trend tests using AAM groups were further performed for these 5 endpoints in females with natural menopause and identified monotonically increasing risk of ever chronic bronchitis, radiographic emphysema, and CVD associated with younger AAM (Supplemental Table 2).

Associations of early menopause with lung function at baseline and its decline over time

Early menopause was associated with lower measurements of FEV1 (−104.8±36.7 mL/s; P<.01), FVC (−78.6±38.2 mL; P=.04), and FEV_1-to-FVC ratio (−2.1%±0.8%; P=.01) at baseline in females with natural menopause (Table 3), but not in those with surgical menopause (Supplemental Table 3). Monotonically decreasing levels of FEV_1, FVC, and FEV_1-to-FVC ratio at baseline were identified to be associated with younger AAM in females with natural menopause (Supplemental Table 4). A total of 3974 spirometry tests were obtained from 824 female smokers with longitudinal spirometry across an average of 9.6 years (Supplemental Table 5). We found that early menopause was associated with an accelerated decline of FEV_1-to-FVC ratio by 44.4% (0.16:0.36) in females with natural menopause (Table 3). A monotonic pattern for a more rapid decline of the FEV_1-to-FVC ratio associated with a younger AAM that was identified through the P value for the trend test is of borderline significance (P=.06) (Supplemental Table 4).

Associations of early menopause with lung cancer risk and mortality

During the follow-up period, a total of 170 incident LC cases (10.2%) and 447 deaths (26.8%) were identified among the 1666 study participants. Early natural menopause was associated with a 40% increased risk of all-cause death with respiratory diseases (hazard ratio [HR], 2.32; 95% CI, 1.52−3.52; P<.001) as the major driver underlying this association (Table 4). Trend tests identified monotonically increasing all-cause and cancer- and respiratory disease−specific mortality associated with younger AAM

TABLE 2
Early vs nonearly menopause and health conditions in females with natural menopause (n = 1038)

Variable	Early (n=198)	Nonearly (n=840)	OR (95% CI)[a]	*P* value
Baseline respiratory symptoms				
Phlegm	101 (51.0)	414 (49.3)	1.07 (0.76−1.49)	.71
Cough	91 (46.0)	319 (38.0)	1.37 (1.00−1.89)	.05
Wheeze	79 (40.1)	244 (29.1)	1.65 (1.18−2.30)	<.01
Dyspnea	97 (49.0)	369 (43.9)	1.21 (0.87−1.67)	.25
Baseline cardiopulmonary comorbidities				
Ever chronic bronchitis	48 (24.2)	131 (15.6)	1.73 (1.19−2.53)	<.01
Radiographic emphysema[b]	95 (49.5)	306 (38.0)	1.70 (1.25−2.31)	<.001
Airway obstruction	88 (44.4)	319 (38.1)	1.31 (0.94−1.83)	.11
Ever cardiovascular diseases[c]	26 (13.1)	60 (7.1)	1.87 (1.13−3.11)	.01
Incident airway obstruction[d]	22 (40.7)	71 (27.4)	2.02 (1.03−3.96)	.04

Data are presented as number (percentage), unless otherwise indicated.

CI, confidence interval; *OR*, odds ratio.

[a] The associations were adjusted for baseline values of age, smoking status, pack-years, overweight or obesity status (dummy variables with nonearly body mass index as the reference), ethnicity (2 dummy variables for African American or other ethnicities with non-Hispanic White as the reference), and history of hormone therapy; [b] Events for emphysema were summed as having radiographic evidence of emphysema (trace, mild, moderate to severe) at baseline computed tomography screening. Ordered logistic regression was used for modeling emphysema risk under the proportional odds assumption; [c] Cardiovascular diseases were defined as having history of myocardial infarction, stroke, or coronary artery bypass or angioplasty; [d] Incident airway obstruction was defined as a newly diagnosed airway obstruction among those without airway obstruction at baseline. Analyzed among 54 and 259 females with early and nonearly menopause, respectively.

Zhai. Early menopause and lung aging in female smokers. Am J Obstet Gynecol 2022.

in females with natural menopause (Supplemental Table 6). Among females with natural menopause, early menopause was associated with twice the risk of LC-specific mortality (HR, 1.94, 95% CI, 1.05−3.58; *P*=.03) and a trend toward increased LC incidence (HR, 1.51; 95% CI, 0.93−2.44; *P*=.09) (Table 4). Similar trends were also observed for LC incidence (HR, 1.56; 95% CI, 0.92−2.66; *P*=.09), LC-specific mortality (HR, 1.97; 95% CI, 0.87−4.47; *P*=.11), and respiratory mortality (HR, 1.57; 95% CI, 0.8−92.80; *P*=.12) in females with surgical menopause (Supplemental Table 7).

Mediation effect of baseline spirometry on the associations between early natural menopause and mortality

Because we observed substantial associations between early menopause and baseline spirometry and mortality among those with natural menopause and because poor lung function is an established factor for mortality, mediation analyses were performed to evaluate potential mediational effects by baseline spirometry on the associations between early menopause and mortality (Table 5). FEV_1, FVC, and FEV_1-to-FVC ratio all had significant mediational effects (all P_{perm} values of <.05). Large mediational effect sizes were observed for all-cause mortality (proportion mediated, 42.4%) and respiratory mortality (proportion mediated, 33.3%) with FEV_1 as the strongest mediators.

Ever hormone therapy and the outcomes

Ever HT use as a binary variable was included in all aforementioned analyses that assessed the effects of early menopause on health outcomes. In females with natural menopause, ever HT use (vs never HT use) was significantly associated with higher baseline FEV_1 levels (58.0±29.6 mL/s; *P*=.05) and higher FEV_1-to-FVC ratio (1.36%±0.66%; *P*=.03) at baseline. In females with surgical menopause, ever HT use (vs never HT use) was significantly associated with higher baseline FEV_1 levels (107.6±44.6 mL/s; *P*=.01), higher FEV_1-to-FVC ratios (1.89%±0.97%; *P*=.05), and lower rates of airway obstruction (OR, 0.65; 95% CI, 0.43−0.99; *P*=.04) at baseline and lower respiratory mortality (HR, 0.61; 95% CI, 0.37−0.99; *P*=.04).

Interaction between early natural menopause and cigarette smoking or body mass index group

We further assessed whether there were interactions between early natural menopause and BMI group or smoking status (baseline smoking status for baseline outcomes and LSS for longitudinal outcomes) on wheezing, bronchitis, emphysema, spirometry, LC incidence, and all-cause, LC-, all cancer-, and respiratory mortality. All *P* values for interaction terms were >.2, except for interactions between early natural menopause and LSS for affecting LC incidence (*P*=.06) and cancer mortality (*P*=.01). Of note, 4 combinations were formed, including noncontinuous smoking and nonearly menopause, noncontinuous smoking and early menopause, continuous smoking and nonearly menopause, and continuous smoking and early menopause. The Kaplan-Meier curve showed that females with early menopause who continued smoking had the highest LC risk and cancer-specific mortality compared with the other 3 combinations (Figure). With females with noncontinuous smoking and nonearly menopause status as the reference, HRs for LC were 0.87 (95% CI, 0.39−1.96; *P*=.73) for noncontinuous smoking and early menopause, 2.05 (95% CI, 1.26−3.35; *P*<.01) for continuous smoking and nonearly menopause, and 4.65 (95% CI, 2.55−8.49; *P*<.001) for continuous smoking and early menopause. With females with noncontinuous smoking and nonearly menopause status as the reference, the HRs for cancer mortality were 0.91 (95% CI, 0.43−1.95; *P*=.81) for noncontinuous smoking and early

menopause, 1.55 (95% CI, 0.94−2.56; P=.09) for continuous smoking and nonearly menopause, and 4.61 (95% CI, 2.63−8.07; P<.001) for continuous smoking and early menopause.

Comment

Principal findings

In a cohort of middle-aged and older postmenopausal female smokers, we found that early natural menopause was associated with worse lung health (ie, chronic bronchitis, radiographic emphysema, and lower FEV_1-to-FVC ratio), accelerated lung aging (ie, incident airway obstruction and a more rapid decline of FEV_1-to-FVC ratio), and higher all-cause and respiratory mortality. Females with early natural menopause who continued smoking had a dramatically increased risk (>4.5-fold) of LC and cancer-specific mortality. However, the aforementioned associations were not observed with surgical menopause.

Results in the context of what is known

Here, early natural menopause was identified to be associated with more severe lung parenchymal destruction (radiographic emphysema). The effect of early natural menopause on lung spirometry is quite large as the differences in baseline spirometry measurements between early and nonearly menopause were equivalent to age-related lung function decline in 2.2 (FVC), 3.1 (FEV_1), and 6.2 (FEV1-to-FVC ratio) years. These equivalents were calculated as the differences between early and nonearly natural menopause (eg, −2.1% for FEV_1-to-FVC ratio) (Table 3) divided by the age-related decline rates (eg, 0.34% per year for FEV_1-to-FVC ratio) (Supplemental Table 5). Furthermore, we identified that early natural menopause was associated with incident airway obstruction and a more rapid decline in FEV_1-to-FVC ratio. In contrast to previous studies that identified a restrictive pattern (a stronger effect on FVC than FEV_1) of menopause-related effects on spirometry,[10,11,15] we found that the effect of early menopause on spirometry followed an obstructive pattern with a larger effect on FEV_1 than FVC, which resulted in the identification of a substantial association between early menopause and FEV_1-to-FVC ratio. This difference is likely because we studied moderate and heavy smokers. Thus, these findings provided strong evidence that early natural menopause is a risk factor for the development of COPD in female smokers.

Time-to-event analyses identified a marked association between early menopause and all-cause mortality in female smokers with natural menopause. Cause-specific analyses further identified that LC and respiratory diseases may be the causes of deaths driving this association. This was different from previous studies, which showed CVD as the main driver for the association between early natural menopause and all-cause mortality.[18,19] Furthermore, the different results could be due to our study of moderate and heavy smokers. Mediation analyses further identified that more than 36% of the magnitude of the associations between early natural menopause and all-cause and respiratory mortality could be explained by FEV_1, further substantiating the importance of maintaining lung health in female smokers with early natural menopause.

The rates of early natural menopause were reported to be <10% in the general population.[12] The early natural menopause rate in PluSS females who were

TABLE 3
Associations between early menopause and spirometry in females with natural menopause (n = 1038)

Analysis	Estimate±SE	*P* value
Baseline spirometry[a]		
FEV1 (mL/s)	−104.8±36.7	<.01
FVC (mL)	−78.6±38.2	.04
FEV_1-to-FVC ratio (%)	−2.1±0.8	.01
Decline of FEV1 (mL),[b] estimate±SE		
Early menopause	−131.6±51.8	.01
TIC	−31.9±3.6	<.001
Early menopause*TIC	0.83±2.28	.72
Decline of FVC (mL),[b] estimate±SE		
Early menopause	−103.8±54.4	.05
TIC	−32.5±4.70	<.001
Early menopause*TIC	3.96±2.95	.18
Decline of FEV_1-to-FVC ratio (%),[b] estimate±SE		
Early menopause	−2.62±1.15	.02
TIC	−0.36±0.10	<.001
Early menopause*TIC	−0.16±0.06	.01

BMI, body mass index; *FEV1*, forced expiratory volume in the first second; *FVC*, forced vital capacity; *LME*, linear mixed effects; *LSS*, longitudinal smoking status; *NHW*, non-Hispanic White; *SE*, standard error; *TIC*, time in cohort.

[a] Linear models were performed to model the outcome of baseline spirometry in 1038 females. Covariates for adjustment included baseline values of age, smoking status, pack-years, height, overweight or obesity status (dummy variables with nonearly BMI as the reference), ethnicity (2 dummy variables for African American or other ethnicities with NHWs as the reference), and history of hormone therapy; [b] LME models were performed among 103 females with early menopause and 428 females with nonearly menopause with ≥2 spirometry tests. Covariates for adjustment included baseline values of age, pack-years, height, overweight or obesity status (dummy variables with nonearly BMI as the reference), ethnicity (2 dummy variables for African American or other ethnicities with NHWs as the reference), and history of hormone therapy and LSS status (former and intermittent smokers with continuous smokers as the reference). Interaction terms of TIC with early menopause, hormone therapy, and LSS status were included in the LME models.

Zhai. Early menopause and lung aging in female smokers. Am J Obstet Gynecol 2022.

TABLE 4
Early menopause and LC risk and mortality in females with natural menopause (n = 1038)

Variable	Menopause	n	Event, n (%)	Person-years	HR (95% CI)[a]	*P* value
LC incidence	Early	198	23 (11.6)	2420.2	1.51 (0.93–2.44)	.09
	Nonearly	840	67 (8.0)	10,931.3		
All-cause mortality	Early	198	63 (31.8)	2565.1	1.40 (1.05–1.86)	.02
	Nonearly	840	200 (23.8)	11,490.8		
LC mortality	Early	198	15 (7.6)	2565.1	1.94 (1.05–3.58)	.03
	Nonearly	840	34 (4.1)	11,490.8		
Cancer mortality	Early	198	27 (13.6)	2565.1	1.74 (1.11–2.74)	.01
	Nonearly	840	67 (8.0)	11,490.8		
CVD mortality	Early	198	21 (10.6)	2565.1	1.38 (0.83–2.29)	.21
	Nonearly	840	62 (7.4)	11,490.8		
Respiratory mortality	Early	198	35 (17.7)	2565.1	2.32 (1.52–3.52)	<.001
	Nonearly	840	65 (7.7)	11,490.8		

CI, confidence interval; *CVD*, cardiovascular disease; *HR*, hazard ratio; *LC*, lung cancer; LSS, longitudinal smoking status.

[a] Cox regression was used to assess the impact of early menopause on risk of lung cancer incidence and all-cause and disease-specific mortality with adjustment for baseline values of age, pack-years, overweight or obesity status (dummy variables with nonearly body mass index as the reference), ethnicity (2 dummy variables for African American or other ethnicities with non-Hispanic Whites as the reference), and history of hormone therapy and LSS status (former and intermittent smokers with continuous smokers as the reference).

Zhai. Early menopause and lung aging in female smokers. Am J Obstet Gynecol 2022.

moderate or heavy smokers was 19.1%, which was consistent with a 2-fold increase in the risk of early menopause in current smokers.[12] Similarly, in a pilot study of smokers (n=318) from the Lovelace Smokers Cohort, early menopause occurred in 19.0% of the 179 participants with natural menopause. However, although the associations between smoking and early menopause have been established,[12] we did not identify any differences in smoking history between early and nonearly menopause probably because of the enrollment of moderate and heavy smokers in the PLuSS cohort. A recent genome-wide association study in >200,000 women of European ancestry identified 290 genetic determinants of natural ovarian aging assessed as age at natural menopause with DNA damage response as the top pathway implicated.[30] Thus, the occurrence of early natural menopause in female smokers as a biomarker of ovarian aging could reflect the outcome of ovarian injury and repair under the chronic insults of toxicants in tobacco smoke.[12] This is consistent with the findings that cigarette smoking was associated with a prolonged and dose-dependent adverse effect on ovarian function.[31,32] Our identification of associations with lung health outcomes may further support early natural menopause as a biomarker predictive of aging of extra ovarian organs, such as lungs in female smokers, potentially because of pan-organ host-environment interactions.

Interactions between cigarette smoking and menopause or early menopause have been reported. A study on British women identified that menopause exaggerated the effect of cigarette smoking on lung function.[13] A recent meta-analysis of 6 cohort studies and 5 case-control studies also found convincing evidence supporting increased LC risk associated with early menopause predominantly in smokers.[33] We found that the effects of continuous smoking on subsequent LC risk and cancer mortality are moderated by early menopause status with more prominent associations found in females with early natural menopause. These studies suggested that females with early natural menopause were most vulnerable to cigarette smoking–induced health effects, including LC. This could be due to early loss of lung health protection from estrogen or simply reflect lower inherent defense capacity against cigarette smoking–induced injury. The latter explanation is more favored because this interaction was only observed in females with natural menopause. Moreover, the substantial interactions between early menopause and cigarette smoking identified in our studies and others[13,33] did not support early natural menopause as merely a proxy for heavier smoking. This was also consistent with the fact that a substantial proportion of the variability (40%–75%) in age at natural menopause is explained by genetic factors in twin and family studies (including population based).[34–37]

Clinical implications

Early menopause suggests a shorter lifetime "exposure" to endogenous hormones (eg, estrogen) associated with female reproductive cycling. Age at baseline was comparable between early and nonearly menopause groups in our study. Thus, our findings suggested that ovarian hormone production has a protective effect on lung health and

TABLE 5
Mediation effect of baseline spirometry on the associations between early menopause and mortality in females with natural menopause

Outcome	Mediator	Early menopause outcome,[a] β (SE); *P* value		Mediation effect	
		Without mediator	With mediator	PM[b]	P_{perm}[c]
Mortality (all cause)	FEV_1	0.33 (0.15); .02	0.19 (0.15); .20	42.4%	<.01
	FVC		0.24 (0.15); .11	27.3%	<.01
	FEV_1/FVC ratio		0.25 (0.15); .09	24.2%	<.01
Mortality (LC)	FEV_1	0.66 (0.31); .03	0.55 (0.32); .08	16.7%	<.01
	FVC		0.56 (0.32); .07	15.2%	<.01
	FEV_1/FVC ratio		0.63 (0.31); .04	4.5%	.013
Mortality (cancer)	FEV_1	0.55 (0.23); .01	0.47 (0.23); .04	14.5%	<.01
	FVC		0.48 (0.23); .03	12.7%	<.01
	FEV_1/FVC ratio		0.51 (0.23); .02	7.3%	<.001
Mortality (respiratory)	FEV_1	0.84 (0.21); <.001	0.56 (0.22); .01	33.3%	<.01
	FVC		0.68 (0.22); <.01	19.0%	<.01
	FEV_1/FVC ratio		0.65 (0.22); <.01	22.6%	<.01

FEV1, forced expiratory volume in the first second; *FVC*, forced vital capacity; *LC*, lung cancer; *PM*, proportion mediated; *SE*, standard error.

[a] Early menopause was modeled in relation to mortality with and without adjustment for potential mediators using Cox regression. Covariates for adjustment included baseline values of age, pack-years, overweight or obesity status (dummy variables with nonearly body mass index as the reference), ethnicity (2 dummy variables for African American or other ethnicities with non-Hispanice Whites as the reference), and history of hormone therapy and LSS status (former and intermittent smokers with continuous smokers as the reference); [b] Proportion mediated following the formula $PM=100\times(\beta-\beta')/\beta$, where β is the total effect of early menopause and β' is the effect estimate of early menopause when controlling for baseline spirometry; [c] P_{perm} is derived after permutation for 200 times. For associations with PM <10%, permutation was performed for 1000 times to generate the P_{perm}.

Zhai. Early menopause and lung aging in female smokers. Am J Obstet Gynecol 2022.

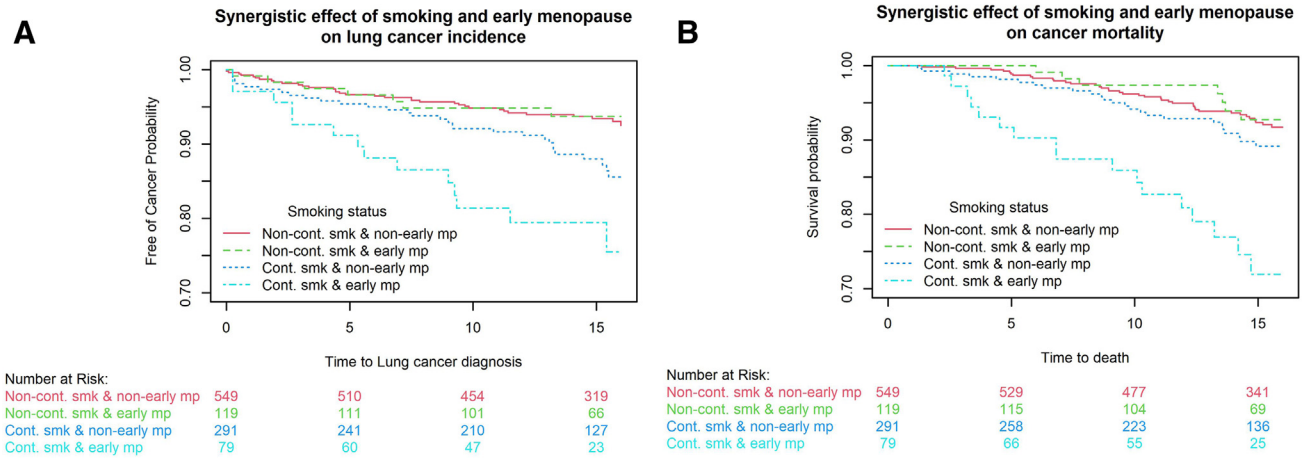
mortality in moderate and heavy smokers at least in those with natural menopause. Of note, 2 mechanisms are likely to explain the estrogen protection on lung health. First, reduced circulating estrogen accompanying the menopause transition results in osteoporosis and suboptimal musculoskeletal function, which may mechanically weaken the expansion and contraction capacity of the thoracic cage during pulmonary ventilation.[22–24] Second, female reproductive hormone metabolism, receptors, and signaling are active in various lung cells, including bronchial epithelium, fibroblasts, and airway smooth muscle cells. Hormones (eg, estrogen) associated with female reproductive cycling are important to maintain optimal lung physiology for lowering airway resistance (eg, bronchodilation)[38,39] and clearance defense (eg, mucociliary clearance).[40,41] Thus, premature loss of pulmonary protection from the natural cycling hormones in females because of early menopause may result in elevated vulnerability to adverse health outcomes induced by cigarette smoking. Our findings of ever HT use associated with greater baseline FEV1 levels in postmenopausal women regardless of menopause types partially supported the "shorter lifetime estrogen exposure" hypothesis. Moreover, HT use was reported to be associated with slower decline rates of FEV_1 and FVC in a duration-dependent manner.[42] However, HT does not provide physiological cycling of sex steroids and does not entirely replicate the premenopausal state. Extended HT beyond coping with menopause symptoms has documented negative consequences, including reduced survival from LC, and current guidelines recommend hormone replacement for a period of 2 to 5 years only.[43–45]

The National Lung Screening Trial demonstrated that smoking cessation and annual low-dose CT screening overall offered the most reduction of LC-specific mortality in heavy smokers.[46–49] Our findings that females with early natural menopause who continued smoking had dramatically (>4.5-fold) increased LC risk and cancer-specific mortality suggested that smoking cessation and LC screening interventions should especially target this group. Smoking cessation is warranted both before menopause to prevent early menopause and after menopause to prevent further health risks, especially in females with early natural menopause.

Research implications

It is important to note that most associations seen in female smokers with natural menopause were not observed in female smokers with surgical menopause in this study. However, the sample size of female smokers with surgical menopause in PLuSS was relatively smaller. Moreover, a subset of female smokers with surgical menopause may still have ovarian estrogen secretion because of receiving hysterectomy only. We expect that associations would differ

FIGURE
Interactions between early natural menopause and continuous smoking affecting LC incidence and cancer mortality



The Kaplan-Meier curve showed that females with early menopause who continued smoking had the highest LC risk (**A**) and cancer mortality (**B**) compared with other 3 combinations. With females with noncontinuous smoking and nonearly menopause status as the reference, the HRs for LC were 0.87 (95% CI, 0.39–1.96; $P=.73$) for noncontinuous smoking and early menopause, 2.05 (95% CI, 1.26–3.35; $P<.01$) for continuous smoking and nonearly menopause, and 4.65 (95% CI, 2.55–8.49; $P<.001$) for continuous smoking and early menopause, and the HRs for cancer mortality were 0.91 (95% CI, 0.43–1.95; $P=.81$) for noncontinuous smoking and early menopause, 1.55 (95% CI, 0.94–2.56; $P=.09$) for continuous smoking and nonearly menopause, and 4.61 (95% CI, 2.63–8.07; $P<.001$) for continuous smoking and early menopause.

CI, confidence interval; *cont*, continuous; *HR*, hazard ratio; *LC*, lung cancer; *mp*, menopause; *smk*, smoking.

Zhai. Early menopause and lung aging in female smokers. Am J Obstet Gynecol 2022.

in female smokers with bilateral oophorectomy vs hysterectomy with or without partial oophorectomy. Testing this hypothesis requires a large cohort of female smokers with detailed surgery information. Moreover, association analyses in female smokers with bilateral oophorectomy would further test the "shorter lifetime estrogen exposure" hypothesis.

Strengths and limitations

The PLuSS cohort enabled us to investigate the effects of early menopause on lung health and aging sequela in a large cohort of female current and former smokers. Moreover, we reported an association between early natural menopause and more severe lung parenchymal destruction and identified LC and respiratory disease as the main driver for early menopause-associated mortality in female smokers. Approximately 92.6% of PLuSS participants were NHWs, and this was consistent with the fact that populations from southwestern Pennsylvania are predominantly NHWs. Thus, it is unknown how well our findings could be generalized to female smokers of Hispanic or Black ethnicity who consume fewer cigarettes but have higher lung disease susceptibility.[50,51] Although the 824 female smokers with ≥2 spirometry tests were not a random sample of the PLuSS cohort, a similar distribution of key variables at baseline (eg, menopause type, early menopause rate, age, smoking status, BMI, and spirometry) between these participants and those with only baseline spirometry minimized the selection bias and supported a high likelihood of generalization of the findings (ie, early natural menopause is associated with incident airway obstruction and FEV_1-to-FVC decline) to other female moderate and heavy smokers.

Conclusions

Our study has provided evidence supporting early natural menopause as a risk factor for malignant and nonmalignant lung diseases and mortality in middle-aged and older female smokers. Our studies have strong public health relevance as preventive strategies, including smoking cessation and chest CT screening,[46,47] should target this population (ie, female smokers with early natural menopause) to improve their postmenopausal health and well-being. More specifically, early natural menopause status should be considered when improving the criteria or risk assessment models for the recommendation of CT screening of LC in female smokers. ■

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