Earlier Age at Menopause, Work and Tobacco Smoke Exposure

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Abstract

Objective—Earlier age at menopause onset has been associated with increased all cause, cardiovascular, and cancer mortality risks. Risk of earlier age at menopause associated with primary and secondary tobacco smoke exposure was assessed.

Design—Cross-sectional study using a nationally representative sample of US women.

Methods—7596 women participants (representing an estimated 79 million US women) from the National Health and Nutrition Examination Survey III were asked: time since last menstrual period, occupation, and tobacco use (including home and workplace secondhand smoke (SHS) exposure). Blood cotinine and follicle-stimulating hormone (FSH) levels were assessed. Logistic regressions for the odds of earlier age at menopause, stratified on race/ethnicity in women 25-50 years and adjusted for survey design, were controlled for age, BMI, education, tobacco smoke exposure, and occupation.

Results—Among 5029 US women ≥ 25 years with complete data, earlier age at menopause was found among all smokers, and among service and manufacturing industry sector workers. Among women age 25-50 years, there was an increased risk of earlier age at menopause with both primary smoking and with SHS exposure, particularly among Black women.

Conclusions—Primary tobacco use and SHS exposure were associated with an increased odds of earlier age at menopause in a representative sample of US women. Earlier age at menopause was found for some women worker groups with greater potential occupational SHS exposure. Thus, control of SHS exposures in the workplace may decrease the risk of mortality and morbidity associated with earlier age at menopause in US women workers.

Introduction

The age of onset of natural menopause in US women has been shown to be related to demographic, reproductive, stress, and health-related behavioral factors.[1] The median age at natural menopause for US women is approximately 51 years, with 5-10% of women menopausal by the age of 45 years.[2-3] Earlier age at natural menopause is associated with an increased risk for all cause, cardiovascular, and cancer mortality, as well as an increased risk for osteoporosis. [4-8]

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In several studies, primary tobacco use has been consistently associated with a significant risk of earlier age at menopause.[9-12] However, the results of the few available studies of secondhand smoke (SHS) exposure have been associated with only a slightly increased to no increased risk of earlier age at menopause.[10-14] These studies have suffered from relatively small sample sizes.

The worksite remains a significant source of SHS exposure for millions of US workers, with levels up to four times that of household.[15-18] Furthermore, occupational SHS exposures are not equally distributed across different worker groups; for example, bartenders, wait staff and other food service workers tend to experience the lowest smoke-free workplace policies.[19] Given the large and increasing number of women in the US workplace, particularly those with high workplace SHS exposure, the potential health effects of occupational SHS exposure need to be explored. For example, several studies have noted stronger lung cancer associations for occupational versus household secondhand smoke exposures, particularly among female workers. [20-21]

This study used a large nationally representative sample of US women workers to evaluate whether the risk of earlier age at menopause was associated with primary and secondary tobacco exposure, including workplace SHS.

Methods

The National Center for Health Statistics (NCHS) developed the National Health and Nutrition Examination Survey (NHANES) to be a representative sample of the entire US civilian population. The NCHS conducted the NHANES III study in two phases: from 1988 to 1991, and from 1991 to 1994. A complex sampling strategy was used to obtain a representative sample of African-Americans, non-Hispanic whites, and Mexican-Americans, ages two months and older.[22] Physical examinations were conducted at mobile examination centers where blood samples and other individual laboratory specimens were collected. Response rates to the physical examinations ranged from 76% to 80%.[23]

Based on the prior work of Cooper et al[3] using the NHANES III data to examine early menopausal status with regards to demographic, behavioral and reproductive characteristics, we eliminated subjects from the analysis if they reported: current use of oral contraceptives, surgical menopause (including bilateral oophrectomy), chemotherapy and radiation, current pregnancy, or breast feeding. Based on the work of Henrich et al,[24] a combination of self-report and follicle stimulating hormone (FSH) levels were used to classify the menopausal status of the NHANES participants. For the initial analyses, women reporting a menstrual period in the past 2 months and with a FSH < 20 IU/L were considered "pre-menopausal"; women reporting no period in the past 2-12 months and with FSH >20 IU/Liter were considered "peri-menopausal"; women reporting no menstrual period in the past 12 months were considered "post-menopausal."

Smoking status was defined as a combination of self-report and serum cotinine levels (Table 1). Survey participants identified as having tried smoking were asked: "Do you smoke cigarettes now?" Those respondents who answered "yes" were classified as current smokers. Additionally, subjects with serum cotinine levels >15 ng/mL, a level which is believed to indicate a current smoker, were also classified as current smokers, irrespective of self-reported smoking status.[25] Survey participants were asked during the interview, "Does anyone who lives [with you] smoke cigarettes, cigars, or pipes anywhere inside this home?" and "How many hours you can smell tobacco smoke at work?" Respondents who answered "yes" to the first question or indicated that they were exposed at work were categorized as being exposed to SHS. In addition, survey participants classified as non-smokers who had a serum cotinine

level at or above the level of detection, were classified as SHS-exposed even if they did not report home or workplace SHS exposures. The comparison group was survey participants who reported being former smokers or never smoking, no home or workplace secondhand smoke, and had cotinine levels below the detection limit. In the NHANES III, serum cotinine was assessed using an isotope dilution, high performance liquid chromatography/ atmospheric pressure chemical ionization tandem mass spectrometric method designed to detect levels as low as 0.050 ng/ml.[26] For analysis purposes, the value for data below the detectable limits was the limit divided by the square root of two.[27]

The identification of subjects' employment status was done through self-report. Survey participants were asked about their work experience during the week prior to their interview. Participants who answered that they were working at a job or business were classified as employed. Using current held job, this permitted classification based on 1980 US Census Codes using a four-category occupational variable commonly employed by the NCHS which included the categories of white-collar (Census codes 003-389), service workers (403-469), farming, fishing, and forestry (473-499), and blue-collar workers (503-889).[28,29] Workers were also grouped into eight industrial sector classifications which are now the focus of the National Occupational Research Agenda (NORA) at the National Institute on Occupational Safety and Health (NIOSH): Agriculture, forestry, fishing; Mining; Construction; Manufacturing; Wholesale and retail trade; Transportation, warehousing, utilities; Services; and Healthcare and social assistance.[30] Of note, these NIOSH NORA industrial groupings ignore the type of work which is done in each sector such that each group may include workers engaged in both blue- and white-collar occupational activities.

To evaluate the issue of the odds for earlier age at menopause, separate logistic regression models for 3 race-ethnicity subcategories (ie. non Hispanic White [Whites], non Hispanic Black [Blacks], and Hispanic [Hispanic] women), weighted and adjusted for the complex sample survey design, were used to analyze the subpopulation of women age 25 to 50 years. Women with missing information or "other races" (i.e. native American and Asian subcategories), the latter for sample size considerations, were eliminated from these analyses. Due to the sample size considerations, the outcome variable, menopause status, had two categories: pre-menopausal, and post-menopausal (i.e. prior peri and post menopausal categories combined). Based on review of the literature and the study dataset, the independent variables in the regression model were: age, body mass index (BMI), education (<12th, 12th and > 12th grade education), tobacco exposure, and occupation. The 0.05 level was used to determine statistical significance, and SAS version 9.1 was used.[31] All analyses were completed with adjustments for sample weights and design effects. This study was approved as Exempt by the University of Miami Human Subjects Committee.

Results

In the NHANES III combined study population of 7832 women aged 25 and older, there were 7596 women with information on their menstrual periods in the past 12 months (representing an estimated 79 million US women). After eliminating subjects reporting other reasons for apparent menopause (ie. current use of oral contraceptives, surgical menopause, chemotherapy or radiation, current pregnancy, breast feeding) and/or missing FSH information, the final study population consisted of 5029 women aged 25 and older. Based on the study smoking and menopausal classifications described above, the majority of women (57%) in the study population were nonsmokers who experienced secondhand smoke; 54% were pre-menopausal (see Table 2). A slight majority (52%) of women were not employed, of whom the majority were post-menopausal, while 74% of the employed women were predominantly pre-menopausal (Table 2).

To examine mean age at menopause, there were 1825 post-menopausal women aged 25 and older with a valid date for age at last menstrual period (see Table 3). Smokers reported a statistically significant earlier mean age (47.17 yrs) at last menstrual period compared to both nonsmokers with SHS exposure (48.59 yrs) and nonsmokers with no SHS exposure (48.55 yrs). There was no statistically significant difference between the age at last menstrual period between nonsmokers with SHS exposure (48.59 yrs) and nonsmokers with no SHS exposure (48.55 yrs). We also examined mean age at menopause among working and non working women. Using the NCHS occupational criteria, although not statistically significant, Service workers experienced the earliest age (46.95 yrs) at menopause, while White collar workers experienced the highest age (48.75 yrs) even compared to unemployed US women. Using the NIOSH industry sector NORA criteria and taking small sample sizes into account, although not statistically significant, Manufacturing workers experienced the earliest age (47.32 yrs), while Wholesale and retail trade workers reported the oldest age (49.17 yrs) of menopause even compared to unemployed US women (48.28 yrs).

In order to examine the odds of earlier age at menopause, there were 2935 women 25-50 years of age. This number was further reduced to 2812 when women with "other" race/ethnicity (ie. Native American and Asian subpopulations), oophrectomy, and missing data in the regression predictors were eliminated from the analysis. The logistic regression models included: age, BMI, education, smoking exposure, and employment; the models evaluated the odds of being early post-menopausal respectively compared to pre-menopausal women. Interactions were examined; due to the significant interactions between race-ethnicity and smoking status, additional stratification of the data was performed by the 3 race-ethnicity subgroups: Whites, Blacks, and Hispanics.

In the logistic regression modeling, as would be expected, increasing age was a significant risk factor for earlier age at menopause for all 3 race-ethnicity subpopulations (see Table 4). For all 3 race-ethnic subpopulations, there was an increased odds of earlier age at menopause with both smoking and with secondhand smoke exposure. Among Blacks, there was a statistically significant 12 times increased odds of earlier age at menopause with tobacco smoke exposure when comparing smokers to nonsmokers with no SHS exposure, and 6 times increased odds compared to nonsmokers with SHS to nonsmokers with no SHS exposure. The odds for earlier age at menopause between smokers and nonsmokers with SHS exposure was elevated 1.8 times, but not significantly. Among Whites, smokers had 1.8 times significantly increased odds compared to nonsmokers with SHS exposure; there was a 2.3 times increased odds for smokers compared to nonsmokers with no SHS, and a 1.3 times increased odds for nonsmokers with SHS compared to nonsmokers with no SHS exposure, although neither was significant. Hispanics also had significant 6.8 times increased odds of earlier age at menopause for smokers compared to nonsmokers with no SHS exposure and a 19 times increased odds for nonsmokers with SHS compared to nonsmokers with no SHS exposure. However, unlike Blacks and Whites, when Hispanic smokers were compared to nonsmokers with SHS exposure, there was a significantly decreased odds of earlier menopause, and Hispanic non smokers with SHS had an increased odds for earlier menopause than Hispanic smokers as well as Hispanic non smokers.

In this logistic model controlling for several variables, BMI was not a significant risk factor for earlier age at menopause for any of the race-ethnic groups. Educational level was not a significant risk factor for earlier age at menopause, although for all 3 race-ethnic groups, there appeared to be an increased odds of earlier age at menopause with fewer years of education. Finally, although not statistically significant, employment appeared to protect against the odds of earlier age at menopause for Blacks and Hispanics, but not for Whites.

Discussion

In this study of a representative sample of all US women, after controlling for other known risk factors, there was an increased odds for earlier age at menopause from exposure to both smoking and secondhand smoking. This was seen most dramatically among Black women who evidenced an apparent dose response relationship with smokers at 12.3 times the odds for earlier age at menopause and non smokers with SHS exposure at 6.7 times the odds for earlier age at menopause compared to nonsmokers with no SHS exposure (Table 4). This more dramatic difference in the Black women may be due to the fact that nicotine and cotinine clearance in Black smokers is reportedly lower than in Whites, leading to a longer cotinine half-life in Blacks particularly since our categorization of tobacco exposure relied heavily on the blood cotinine level as well as self-report (Table 1).[32,33]

Prior studies have shown at least a 50% increased risk for earlier age at menopause among smokers, [9-11] however the association between the risk for earlier age at menopause and exposure to secondhand tobacco smoke at home and in the workplace has been equivocal. [10-14] This study using a large nationally representative sample of the entire US population, demonstrated an increased odds for earlier age at menopause with both primary tobacco use and with second hand smoke exposure from the workplace and home in nonsmokers. Prior studies of menopausal risk and secondhand smoke have noted that when "ever" or "former smokers" were removed from the analyses such that nonsmokers are "never smokers," the association between earlier age at menopause and SHS exposure disappeared.[11] However, in our study population, when former smokers were removed and the analyses repeated, these same associations were seen although with less statistical significance due to smaller sample sizes (data not shown).

Although with increasing numbers of women in the US workforce, there has also been very little research into the effect of occupation on menopause. Higher socio-economic class has been shown to be associated with later age at menopause,[1-3] and was confirmed in this study with white collar workers and higher education. In a study of 1594 employed French women, in addition to the usual risk factors, Cassou et al[12] found that certain job stressors (i.e. difficult work schedules and a high stress job) might be related to an increased risk of earlier age at menopause. In addition to finding the same association between increased age and higher socio-economic class, our study is the first to examine the age at menopause by occupation and industry categories, suggesting an earlier age at menopause for women in service occupations and the manufacturing industry, both employment categories with higher reported SHS exposures.

Strengths and Limitations

There were several study limitations including the use of cross-sectional self-reported data. However, we were able to include objective data to substantiate the self-report: in the case of menopause status, serum FSH data; in the case of smoking status, serum cotinine. Of note, serum cotinine has a half life of 16-18 hours, therefore it cannot be considered a measure of chronic exposure to secondhand smoke,[32,33] particularly since only a single cotinine level was available for the NHANES participants. Thus, it is likely that some unknown proportion of our non-tobacco smoke exposure workers had a significant history of secondhand smoke exposure. Of note, since only home and workplace self-report of SHS data were collected, it was not possible to obtain reports of exposures in other settings such as in cars or bars (as well as other sources of nicotine leading to cotinine in the urine, such as food).[34] Additionally, the NHANES III does not collect information on historical exposures to SHS, including childhood exposures. Incomplete characterization of current and former exposure the SHS may have biased the models. For example, misclassification, perhaps in combination with relatively small analytic sample sizes for some of the sub-group analyses, may explain the apparently

paradoxical finding of a decreased odds of earlier age at menopause for Hispanic smokers compared to Hispanic non-smokers with SHS exposure; it is possible that some of the apparent nonsmoker with SHS exposure Hispanic women were really low exposure smokers, or had high levels of SHS exposure outside of their home and work or through diet. Given these limitations, the effects of tobacco smoke exposure on the initiation of earlier age at menopause needs further study. Additionally, these studies should employ longitudinal study designs and include adequate numbers of racial and ethnic group sub-populations since these groups may be particularly vulnerable to the effects of tobacco smoke exposure.

Conclusions

With a total economic cost of at least 10 billion dollars annually, SHS has been established to cause premature death and disease in adults who do not smoke.[32,33,35] Additional research indicates that this may be an underestimate since it does not include costs associated with health outcomes not yet determined to be causally associated with SHS.[36] Our findings suggest that the additional costs of earlier age at menopause should be added to the costs of SHS exposure, in terms of increased risks for overall, cardiovascular and cancer mortality as well as increased risk for osteoporosis.

Since the worksite remains a significant source of SHS exposure for millions of US women workers,[15-18] increased efforts to implement smoke-free workplace policies in all US workplaces are recommended. In addition, further research into the risks of women in particular occupational and industries for earlier age at menopause is also recommended, particularly those at increased risk for occupational SHS. Finally, the development of worksite-based programs is needed to reach the millions of employed women smokers.[37,38] Not only will such approaches lower employer health care and productivity costs, but may produce the additional benefit of lowering the number of women entering into premature menopause. [39-41]

Acknowledgments

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Additional Key words

SHS

Secondhand smoke

NORA

National Occupational Research Agenda

NHANES 3

National Health and Nutrition Examination Survey III

Table 1

Tobacco exposure classification

Smoking status	Self report smoking	Self report SHS (Home or work)	Serum cotinine level
Smoker[†]	Yes or No	Yes or No	>15 ng/mL
Non Smoker with SHS[*†]	No	Yes or No	≥Detection limit to <15 ng/mL
Non Smohker with no SHS[*]	No	No	< Non detection limit

[*] includes never and former smokers

[†] Participants who self-identify as smokers or who have serum cotinine levels >15 mg/mL are classified as smokers

[‡] Participants who report any SHS exposure or who fall within the cotinine range are classified as non-smokers with SHS exposure

Table 2

All US Women classified by menopausal status with smoking status and employment status

Smoking Status	Menopause Status			Total
	Pre (%)	Peri (%)	Post (%)	
Smoker	807 (63%)	61(5%)	418(33%)	1286
Nonsmoker with Secondhand Smoke Exposure	1553 (54%)	139(5%)	1171 (41%)	2863
Nonsmokers with no Secondhand Smoke Exposure	378(43%)	22 (3%)	480 (55%)	880
Total	2738	222	2069	5029
Employment status				
No	964 (37%)	78 (3%)	1581 (60%)	2623
Yes	1774 (74%)	144 (6%)	488 (20%)	2406
Total	2738	222	2069	5029

Table 3

Mean age at menopause of all US Women classified by age at last menstrual period with smoking status and NCHS Occupational and NORA Industrial Sector status

Smoking Status	N	Mean Age Last Period	SE	95% CI
Smoker	365	47.17	0.48	46.22-48.13
Nonsmoker with Secondhand Smoke Exposure	1033	48.59	0.27	48.06-49.13
Nonsmokers with No Secondhand Smoke Exposure	427	48.55	0.46	47.62-49.48
NCHS Occupational Code				
White Collar	234	48.75	0.34	48.06-49.34
Service	154	46.95	0.74	45.46-48.44
Farm Worker[*]	8	47.64	1.25	*
Blue Collar	66	47.78	1.06	45.67-49.89
Unemployed	1363	48.28	0.26	47.76-48.81
NORA Industrial Sector				
Agriculture, Forestry, Fishing	11	48.41	0.87	*
Construction	2	44.55	0.67	*
Healthcare and Social Assistance	82	47.84	0.75	46.35-49.34
Manufacturing	69	47.32	1.26	44.80-49.84
Mining	1	56.00	0.00	*
Services	207	48.27	0.38	47.51-49.02
Transportation, Warehousing, Utilities	16	48.14	1.78	*
Wholesale and Retail Trade	74	49.17	0.52	48.13-50.22
Unemployed	1363	48.28	0.26	47.76-48.81

(Only includes with women with valid data for date at last menstrual period)

[*] estimate unstable due to small sample size

Table 4

Logistic regression model evaluating the odds of earlier age at menopause among the study population of US women age 25-50 years

	Whites (n=943)		Black (n=988)		Hispanic (n=881)	
	Race-Ethnic Subgroup					
Independent Variable	OR	95% CI	OR	95% CI	OR	95% CI
Age (years)	**1.38**	**1.27-1.49**	**1.30**	**1.21-1.38**	**1.41**	**1.28-1.54**
BMI	0.99	0.93-1.05	1.00	0.96-1.04	1.07	0.99-1.16
Education						
<12 years versus 12 years	1.18	0.50-2.76	1.10	0.50-2.40	2.06	0.98-4.33
>12 years versus 12 years	0.60	0.27-1.30	0.88	0.48-1.63	0.99	0.25-3.97
<12 years versus >12 years	0.51	0.39-1.66	0.80	0.39-1.66	0.48	0.18-1.27
Smoking Status *						
Smoker versus no SHS exposure	2.34	0.70-7.82	**12.34**	**3.03-50.21**	**6.80**	**1.92-24.11**
SHS exposed *vs.* non-SHS exposed	1.25	0.41-3.78	**6.65**	**1.45-30.40**	**19.08**	**5.96-61.07**
Smoker vs. SHS-exposed	**1.87**	**1.08-3.24**	1.86	0.99-3.50	**0.36**	**0.18-0.70**
Employment Status						
Employed	1.38	0.65-2.93	0.73	0.39-1.35	0.80	0.31-2.04
Not Employed	1.00		1.00			

*
SHS-exposed and non-SHS exposed categories are both non-smoking