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Environmental tobacco smoke and risk of late-diagnosis incident fibroids in the Study of Women's Health across the Nation (SWAN)

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Objective: To assess the longitudinal relationship of environmental tobacco smoke (ETS) exposure during midlife, and its interaction with active smoking, with the risk of late-diagnosis incident uterine fibroids during the menopausal transition.
Design: Thirteen-year prospective cohort study.
Setting: Not applicable.
Patient(s): Community-based, multiracial/ethnic cohort of 2,575 women aged 42 to 52 years at baseline, undergoing the menopausal transition.
Intervention(s): Questionnaire and blood draws.
Main Outcome Measure(s): Discrete-time proportional odds models were used to estimate the conditional odds ratio (OR) and 95% confidence interval (CI) of incident fibroids, adjusted for menopausal status, race/ethnicity, study site, age, education, estradiol levels, sex hormone use, body mass index, timing of blood draw, age at menarche, alcohol use, and smoking status and pack-years.
Result(s): As part of SWAN, at each near-annual study visit, ETS exposure, smoking, and fibroid occurrence were self-reported via questionnaire, and blood draws were collected. Women who were exposed to ETS ($\geq$1 person-hour/week) had 1.28 (95% CI, 1.03, 1.60) times the adjusted odds of incident fibroids in the ensuing year compared the unexposed. The odds were elevated in never smokers (adjusted OR 1.34; 95% CI, 1.06, 1.70) and former smokers (adjusted OR 2.57; 95% CI, 1.05, 7.23).
Conclusion(s): In midlife, ETS exposure was associated with an increased risk of late-diagnosis incident fibroids in women undergoing the menopausal transition. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Environmental tobacco smoke, secondhand smoke, uterine fibroids, leiomyomas, longitudinal study

Discuss: You can discuss this article with its authors and with other ASRM members at

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Environmental tobacco smoke (ETS; secondhand smoke or passive smoke) is a public health burden that has received considerable regulatory scrutiny over the past few decades (1). Although the prevalence of ETS exposure has declined since the 1990s due to regulatory bans on indoor smoking, the estimated annual economic costs attributed to smoking and ETS exposure continues to rise, approaching $300 billion in the United States in 2014 (2). Most population-based studies have focused on respiratory outcomes, but ETS has also been

associated with adverse reproductive health outcomes in women, including low birthweight and preterm births, and inconsistently with decreased fertility (3–5).

Uterine fibroids, benign tumors of the myometrium that typically emerge during premenopause and perimenopause, are detected in approximately 70% to 80% of women (6). Symptoms include pelvic pain, abnormal uterine bleeding, decreased fertility, and complications in pregnancy (6). The strongest established risk factors include being African-American, obese, nulliparous, premenopausal, and a user of hormone replacement therapy (7–12). Conversely, active cigarette smoking has been associated with decreased risk of fibroids in some studies (13–15), although another study found positive associations with diffuse fibroids (16). Preventive strategies are desirable because the therapeutic options are limited, and hysterectomy remains the first-line treatment (6). Myomectomy of fibroids is another surgical option for women who want to become pregnant, but recurrence is still possible.

Late-diagnosis fibroids are an underinvestigated health burden in perimenopausal and postmenopausal women because most cases are diagnosed earlier in the life course. The contributions of ETS to fibroid development have yet to be firmly established, despite possible associations with active smoking. To advance the understanding of the interrelationship between ETS, active smoking, and risk of late-diagnosis fibroids, we leveraged data from the Study of Women's Health across the Nation (SWAN), a multiracial/ethnic cohort of midlife women undergoing the menopausal transition. The objective of this study was to assess the longitudinal relationship between ETS exposure in midlife, its interaction with active smoking, and the risk of late-diagnosis incident uterine fibroids. We hypothesized that ETS exposure would be associated with an increased risk of developing uterine fibroids, which would be further elevated in former and current smokers.

MATERIALS AND METHODS

Study Population

The characteristics of SWAN have been described elsewhere (17). Briefly, SWAN is a multiracial/ethnic prospective cohort study of women undergoing the menopausal transition. SWAN enrolled 3,302 eligible women from seven sites across the United States. At baseline, the participants were aged 42 to 52 years, were premenopausal or early perimenopausal, reported a recent menstrual period, had an intact uterus and at least one ovary, were not pregnant or lactating, and had not recently used exogenous hormones. Since 1996 the participants have been evaluated at near-annual in-person visits, using self-administered questionnaires and interviews to collect demographic, medical, reproductive, and anthropometric information. The institutional review boards of all participating institutions approved the SWAN core study. All participating women provided written informed consent.

The current analyses used a longitudinal design with near-annual repeated measures of ETS exposure, covariates, and fibroid occurrence throughout 13 years of follow-up evaluation. Women who reported any cancer diagnosis before baseline were excluded. Subsequently, there were 3,217 women with ETS exposure data at baseline. The survival analyses further excluded women who reported having fibroids before baseline. The resulting analytic sample size was 2,575 women. During the follow-up, women who reported having a hysterectomy or incident fibroids or who had died, or were permanently lost to follow-up evaluation since the last visit were censored.

Outcome Assessment: Uterine Fibroids

From visits 0 to 3, the occurrence of fibroids was assessed by asking, "Since your last study visit, has a doctor, nurse practitioner, or other health care provider told you that you had fibroids, benign growths of the uterus or womb, or treated you for them". From visits 4 to 13, occurrence was assessed by asking, "Since your last study visit, have you had fibroids (benign growths in the uterus or womb)?" Medical record abstractions for a subset of 99 women who underwent hysterectomy were analyzed using binomial proportions tests for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), against verified gross and histologic clinical findings.

Exposure Assessment: Environmental Tobacco Smoke

Time-varying ETS exposure was assessed at baseline and at visits 3, 7, 8, and 9 using seven questions adapted from a validated survey (18). Participants were asked the number of active smokers at home, work, and social settings, days of ETS exposure in the past week, and daily hours of ETS exposure, at home, work, and other social settings. Based on a previous study, cumulative ETS exposure in the past 7 days (person-hours/week) was calculated as follows: (No. of smokers at home) * (Hours/day of ETS exposure at home) * (No. of days of ETS exposure in past 7 days at home) + (No. of smokers at work) * (Hours/day of ETS exposure at work) * (No. of days of ETS exposure in past 7 days at work) + (Hours/day of ETS exposure at other settings) * (No. of days of ETS exposure in past 7 days at other settings) (18). Legislation has prohibited smoking at work and certain public settings in some states since the 1990s, and these bans would likely generate geographic variability in ETS exposure, which was analytically desirable.

Serum Estradiol Measurements

Total 17β-estradiol (E_2) and sex hormone-binding globulin (SHBG) were measured in near-annual intervals using an automated chemiluminescence system-180 analyzer (Bayer Diagnostics) as previously described elsewhere (19). During premenopause and early perimenopause, the timing of the blood draw was "in window" if the blood was drawn between days 2 and 5 of a menstrual cycle, and "out of window" otherwise. The level of bioavailable E_2 was presented as a unitless index calculated as the ratio of total E_2 (nM) to SHBG (nM): 100 $\times$ (Total E_2 (pg/mL) $\times$ [0.003671 nM per 1 pg/mL E_2])/ SHBG (nM) (20). The E_2 levels were measured because of their