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Cigarette Smoking, Smoking Cessation and Risk of Hearing Loss in Women

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Abstract

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Data Access, Responsibility, and Analysis: BML and SGC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest: Dr. G. Curhan serves as a consultant to Decibel Therapeutics, AstraZeneca, Shire/Takeda, Allena Pharmaceuticals, RenalGuard, Orfan Biotech, Dicerna, and Merck. He is an employee of OM1, Inc. He receives royalties from UpToDate for being an author and section editor. Dr. S. Curhan served as a consultant to Decibel Therapeutics. The other authors have no competing interests to declare.

Ethical Approval: This study was approved by the Partners Healthcare Institutional Review Board. Completion of the self-administered questionnaire was considered implied informed consent

Background: Previous studies demonstrated higher risk of hearing loss among cigarette smokers, but longitudinal data on whether the risk is influenced by smoking cessation are limited. We prospectively investigated relations between smoking, smoking cessation and risk of self-reported moderate or worse hearing loss among 81,505 women in the Nurses' Health Study II (1991-2013)

Methods: Information on smoking and hearing status was obtained from validated biennial questionnaires. Cox proportional hazards regression was used to estimate multivariable-adjusted relative risks (MVRR,95%CI).

Results: During 1,533,214 person-years of follow-up, 2760 cases of hearing loss were reported. Smoking was associated with higher risk of hearing loss and the risk tended to be higher with greater number of pack-years smoked. Compared with never smokers, the MVRR(95% CI) among past smokers with 20+ pack-years of smoking was 1.30(1.09,1.55) and 1.21(1.02,1.43) for current smokers. The magnitude of elevated risk diminished with greater time since smoking cessation. Compared with never smokers, the MVRR among smokers who quit <5 years prior was 1.43(1.17,1.75); 5-9 years prior was 1.27(1.03,1.56); 10-14 years prior was 1.17(0.96,1.41); and plateaued thereafter. Additional adjustment for pack-years smoking attenuated the results.

Conclusions: The higher risk of hearing loss associated with smoking may diminish over time after quitting.

Keywords

hearing loss; smoking; smoking cessation; women

INTRODUCTION

Recent estimates from the National Health and Nutrition Examination Survey suggest that 48 million US adults suffer from hearing loss.¹ Hearing loss may be associated with impaired communication, decreased quality of life, depression,²⁻⁴ and cognitive decline,^{5, 6} thus understanding how modifiable factors may influence risk could provide new insights into possibilities for prevention or delay of acquired hearing loss.

Lifestyle factors such as smoking have been associated with acquired hearing loss. Cigarette smoking is highly prevalent; an estimated 15% of U.S. adults are active smokers.⁷ Evidence suggests smoking is associated with damage to the outer hair cells of the cochlea,⁸ increased oxidative stress due to generation of reactive oxygen species,⁹ and elevated systemic inflammatory markers.¹⁰ Several toxins found in cigarette smoke, including toluene, benzene, and carbon monoxide, have been associated with hearing loss.^{11, 12} Current smoking has been shown to be associated with hearing loss in several populations,¹³ but most studies have been cross-sectional. Findings from studies of the relation among past smokers, or the amount and duration of smoking, have been inconsistent.¹⁴⁻²⁰ Few studies have prospectively examined how the magnitude of the risk is influenced by smoking cessation and time since quitting.^{17,21} Therefore, we prospectively investigated the relation between the amount and duration of smoking, time since smoking cessation, and risk of self-reported moderate or worse hearing loss among 81,505 women in the Nurses' Health Study II (NHS II) over a 22-year follow-up period. The large cohort size and extensive longitudinal

data collection allow for a robust evaluation of the associations of cigarette smoking, smoking cessation, and risk of hearing loss.

MATERIALS AND METHODS

Study participants

The Conservation of Hearing Study (CHEARS) investigates risk factors for hearing loss among participants in the NHS II, which began in 1989 when 116,430 female registered nurses aged 25-42 years completed a baseline questionnaire. Questionnaires have been administered biennially and the follow-up over 30 years is >90% of eligible person-time. The baseline year of our analysis was 1991, the year when information on many of the covariates considered in our multivariable analyses was first ascertained.

Of the 87,381 women who answered the 2009 or 2013 questionnaires that collected information on hearing, we excluded those who reported onset of a hearing problem before baseline (n=1290), those who did not answer the hearing questions (n=948), those with missing information on smoking (n=2515), and those who reported a history of cancer other than non-melanoma skin-cancer (due to possible exposure to ototoxic chemotherapeutic medications; n=1123). The total number of women included in the analysis was 81,505. This study was approved by the Partners Healthcare Institutional Review Board.

Ascertainment of smoking

On the baseline questionnaire and every two years thereafter, participants were asked about their current and past smoking habits, including the average number of cigarettes smoked per day. Data were updated every two-year questionnaire cycle, when available. Participants with missing information on smoking status over any questionnaire cycle were skipped for that time period, but were allowed to re-enter the analysis in subsequent time periods. Smoking assessed in this manner in this and similar cohorts has been associated with higher risk of cardiovascular disease,^{22, 23} breast cancer,²⁴ and mortality associated with smoking-related diseases.²⁵ Smoking behaviors that were assessed included smoking status (never, past, current) and pack-years, a composite variable that combined smoking status and amount of smoking (never, 1–9, 10–19, and 20 pack-years). Pack-years of smoking is a measure of the amount an individual has smoked over time and was calculated by multiplying the number of packs of cigarettes per day (20 cigarettes=1 pack) by the number of years the participant smoked. For past smokers, time since smoking cessation was calculated as the difference between current age and age at smoking cessation.

Ascertainment of hearing loss

The primary outcome in our study was self-reported moderate or worse hearing loss. In 2009, participants were asked: “Do you have a hearing problem?” (no; mild; moderate; severe), and if so: “At what age did you first notice a change in your hearing?” On the 2013 questionnaire, women were asked: “Which best describes your hearing?” (excellent; good; a little hearing trouble; moderate hearing trouble; deaf), “Have you noticed a change in your hearing?” and, if so: “At which age did you first notice a change in your hearing?” We defined cases of hearing loss as women who reported a moderate or worse hearing problem,

with date of onset after 1991 (the baseline year of our study). Participants who reported a “mild” hearing problem on the 2009 questionnaire were skipped in the analysis from the time of onset of their “mild” hearing problem and re-entered the analysis upon subsequent report of a hearing problem moderate or worse in severity on the 2013 questionnaire. We *a priori* chose to examine moderate or worse hearing loss to minimize misclassification and to identify cases of most clinically meaningful hearing loss.

Previous studies have demonstrated that self-reported hearing loss is a relatively reliable indicator of hearing loss when compared with hearing loss diagnosed by audiogram.^{26–30} A validation study of self-reported hearing loss assessed by a single question in women less than 70 years of age compared with hearing loss ascertained by audiometry demonstrated sensitivity of 95% for detecting moderate hearing loss, defined as pure tone averages at 0.5, 1, 2, 4 kHz of greater than 40 dB HL in the better hearing ear, and sensitivity of 100% for detecting severe hearing loss, defined as pure tone averages at 0.5, 1, 2, 4 kHz of greater than 60 dB HL in the better hearing ear; the specificities were 65% and 64%, respectively.³⁰ Associations between several other risk factors and hearing loss have been demonstrated using these assessment methods.^{31–34}

Ascertainment of covariates

Covariates were selected based on factors purported to be associated with hearing loss. Factors considered included age,³⁵ race,³⁵ body mass index,³⁶ waist circumference,³⁶ alcohol intake,^{15, 37} *trans*-fat,³ long-chain omega-3 polyunsaturated fatty acids,³⁸ folate,^{39, 40} beta-carotene,⁴⁰ beta-cryptoxanthin,⁴⁰ vitamin B₁₂,⁴¹ vitamin C,⁴⁰ magnesium,⁴² physical activity,^{36, 43} hypertension,³¹ diabetes,⁴⁴ tinnitus,^{45, 46} acetaminophen use,^{32, 47} and non-steroidal anti-inflammatory drug use.^{32, 47} Covariates were updated based on information provided on the biennial questionnaires. Information on dietary intake was obtained from semiquantitative food frequency questionnaires that were administered every four years. The validity and reproducibility of data derived from the food frequency questionnaires have been reported.^{48, 49} Many of the covariates included in our analyses have been shown to be valid measures in this and other similar cohorts.^{50–52}

Hearing Study Supplemental Questionnaire (HSSQ)

In 2012, a detailed hearing-related questionnaire was administered in a sub-cohort of 33,102 women in NHS II. Participants were asked about previous evaluation for hearing loss, laterality of hearing loss when applicable, lifetime noise exposure, and potential identifiable causes of hearing loss (e.g. ototoxic medications, ear trauma, otosclerosis, cholesteatoma, Meniere’s disease, chronic ear infection).

Statistical analysis

All analyses were performed in a prospective manner. Person-time of follow-up was calculated from the date of return of the 1991 questionnaire until the date of self-reported moderate or worse hearing loss or end of follow-up in 2013. Participants who reported cancers other than non-melanoma skin cancer during follow-up were censored when reported. Age- and multivariable-adjusted relative risks were calculated using Cox proportional hazards regression models to adjust for potential confounders. The Anderson-

Gill data structure was used to deal with time-varying covariates and left truncation in an efficient manner.⁵³ We performed analyses stratified by <10 vs 10 pack-years (the median number of pack-years smoked) to examine whether the association between smoking cessation and hearing loss differed by pack-years smoked. We performed additional analyses among participants who had completed the Hearing Study Supplemental Questionnaire for whom we had information on otologic conditions and noise exposure history (n= 24,495). P-values are all two-sided, with 95% confidence intervals for all relative risks. SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

RESULTS

The baseline characteristics of participants according to smoking status in 1991 are shown in Table 1. At baseline, 66.5% of participants were never smokers, 22.4% of participants were past smokers, and 11.1% of participants were current smokers. The mean ages of never, past, and current smokers were 35.9, 37.1, and 36.6 years, respectively, and the participants were predominantly white (>95%). Women who were past or current smokers tended to consume more alcohol than never smokers.

During 1,533,214 person-years of follow-up (1991-2013), 2760 cases of moderate or worse hearing loss were reported. Smoking was associated with higher risk of hearing loss among both past and current smokers, and the risk tended to be greater with greater number of pack-years smoked (Table 2). Among past smokers, there was an overall trend towards higher risk of moderate or worse hearing loss among women with greater pack-years smoking history (p-trend <0.001). Among current smokers, there was also an overall trend towards higher risk of moderate or worse hearing loss among women with greater pack-years smoking history (p-trend 0.02).

Among past smokers, the magnitude of the elevated risk tended to diminish with greater time since smoking cessation over the first 10 to 14 years since quitting, and then plateaued (Table 3). Compared with never smokers, there was an overall trend towards lower magnitude of moderate or worse hearing loss risk among past smokers with greater duration since quitting smoking (p-trend <0.001). Further adjustment for pack-years of smoking attenuated the results. There was no significant interaction (p=0.8) when we examined the association stratified by the median of 10 pack-years of smoking (results not shown).

In additional analyses among participants who provided information on the Hearing Study Supplemental Questionnaire, we excluded women with otologic disease or other diagnosed etiologies for hearing loss and further adjusted for loud noise exposure and impulse (e.g. gunfire) noise exposure. The results were similar. For example, among past smokers, the multivariable-adjusted relative risk (MVR, 95% CI) of moderate or worse hearing loss among women with a history of smoking 1-19 pack-years was 1.12 (0.87, 1.30), and 20+ pack-years was 1.41 (1.09, 1.82), compared with never smokers (p-trend=0.004). The association between smoking and risk of moderate or worse hearing loss did not vary by noise exposure (p-interaction >0.3)(results not shown).

DISCUSSION

In this large, prospective cohort of women in the U.S., smoking, whether past or current, was associated with higher risk of hearing loss and the magnitude of the risk was greater among those with more pack-years of smoking (greater lifetime cigarette tobacco exposure). Among past smokers, the magnitude of the elevated risk tended to diminish with greater time since smoking cessation.

Several proposed mechanisms might underlie the relation between smoking and hearing loss. Smoking is associated with the generation of reactive oxygen species and increased oxidative stress,^{9, 54} elevated systemic inflammatory markers,¹⁰ and damage to cochlear outer hair cells.⁸ Smoking related impairment of the redox system is associated with cochlear hypoxia, cell injury, and impairment of the active mechanisms of outer hair cells.^{9, 54–57} Components of cigarette smoke, such as toluene, benzene, and carbon monoxide, have also been associated with hearing loss.^{11, 12} Cigarette smoke exposure may also impair vascular endothelial function, increase the risk of atherosclerosis and increase blood viscosity, and compromise oxygen delivery to the cochlea.^{58–60} Nicotine from tobacco may induce vasoconstriction, impair tissue perfusion and lead to cellular dysfunction.^{59–61}

Our findings that smoking is associated with higher risk of hearing loss are consistent with previous epidemiologic studies,^{17, 2114–2013} however, most studies have been cross-sectional and many did not evaluate the amount of smoking, particularly among former smokers. In our longitudinal study, we observed that the magnitude of the risk was larger among women with greater number of pack-years smoked, suggesting that cumulative lifetime exposure to smoking may contribute an elevated risk of hearing loss among past as well as current smokers.

Among past smokers, time-dependent benefits to smoking cessation have been demonstrated, including reductions in the elevated risk of stroke⁶² and cancer⁶³ with greater time since smoking cessation. To our knowledge, only 2 previous longitudinal studies have examined whether the duration of smoking cessation influences the risk of hearing loss. A large epidemiologic study comprised primarily of male industrial workers in Japan (n = 34,912) found the magnitude of the excess risk of high frequency hearing loss, defined as a pure-tone hearing threshold >40 dB at 4 kHz in at least one ear, was lower among past smokers (HR 1.2, 95% CI 1.0, 1.3) than among current smokers (HR 1.6 (1.4, 1.7), even among individuals who quit <5 years before baseline; however, the amount of smoking (e.g. pack-years) was not examined.²¹ In the Epidemiology of Hearing Loss Study (n = 1678), the risk of hearing loss, defined as a pure-tone average (PTA) of hearing thresholds at 0.5, 1, 2 and 4 kHz > 25 decibels Hearing Level (dB HL) in either ear, was significantly higher among current smokers (HR 1.36, 95% CI 1.05, 1.77), but not among past smokers (HR 1.13, 95% CI 0.94, 1.37), compared with never smokers. Among past smokers, there was a suggestion that the risk declined with greater time since smoking cessation (p-trend = 0.013), but the categorization time since quitting was limited to <5 years and 5+ years since smoking cessation, and the confidence intervals for the point estimates were wide. Notably, in that study, no association between pack-years smoked and risk of hearing loss was observed.¹⁷

Strengths of our study include the large study population and long-term follow-up, as well as the prospective assessment of smoking habits – which likely minimizes reporting errors and misclassification is most likely to be nondifferential and represents a bias toward the null. We adjusted for potentially confounding variables, many of which have previously been demonstrated to be well-reported in this cohort;^{52, 67} however, we cannot exclude the possibility of residual confounding. Our study has limitations. Information on smoking was collected by self-report, but self-reported smoking has been shown to be largely accurate in various study populations.^{64–66} We did not have information on noise exposure on all of the participants. However, in analyses among the subgroup of women for whom we had information lifetime noise exposure, adjustment for noise did not materially change the results. Information in this study was prospectively collected over 22 years, and information provided by this and similar cohorts has been shown to be highly reliable.^{48–50, 52, 68} The outcome of our study was self-reported moderate or worse hearing loss. Although pure-tone audiometry is considered the gold standard for diagnosis of hearing loss, self-reported hearing loss has been shown to be a reliable indicator^{26–30} and the sensitivity and specificity questionnaire-based assessment increased with greater severity of hearing loss.^{29, 30} Our study population was comprised of predominantly white women, which may limit generalizability.

In this large prospective study among women, both past and current smoking were associated with higher risk of moderate or worse hearing loss and the magnitude of the elevated risk was larger with greater number of pack-years smoked. The observation that the amount of smoking influences risk even among former smokers may provide insight into mechanisms that underlie the adverse influence of cigarette smoke on hearing health. Notably, the risk may diminish with greater duration of smoking cessation. Cigarette smoking is a well-established risk factor for many adverse health outcomes, and these findings contribute to the body of evidence that supports the benefits of quitting smoking.

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Clinical Significance

- Past and current smoking were independently associated with higher risk of moderate or worse hearing loss
- The magnitude of the elevated risk of hearing loss was larger with greater number of pack-years smoked.
- There was a trend towards diminished risk of hearing loss with greater duration of smoking cessation.

Table 1.

Age-Standardized Baseline (1991) Characteristics of Participants According to Smoking Status, Nurses' Health Study II

Characteristic	Never Smoker (n=54191)	Past Smoker (n=18240)	Current Smoker (n=9074)
Age, years ^a	35.9 (4.7)	37.1 (4.5)	36.6 (4.6)
Body mass index, kg/m ²	24.5 (5.2)	24.6 (5.2)	24.5 (5.1)
Waist circumference, cm ^b	77.8 (12.6)	78.0 (12.5)	78.8 (13.2)
White race, %	95.2	97.5	96.9
Physical activity, METs/week	20.5 (26.1)	22.5 (28.5)	19.8 (27.6)
Alcohol consumption, g/day	2.4 (4.9)	4.4 (6.8)	5.3 (9.2)
Hypertension, %	6.2	6.2	6.1
Diabetes, %	0.8	0.7	0.7
Tinnitus, %	8.9	9.7	8.1
Regular NSAID use			
1-3 days/week, %	56.8	58.0	56.7
4+ days/week, %	8.0	9.2	10.2
Regular acetaminophen use			
1-3 days/week, %	52.1	49.3	48.1
4+ days/week, %	3.5	3.7	5.0

Values are means (SD) or percentages and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding.

^aValue is not age adjusted

^bValue from the year 1993

METs = metabolic equivalents from recreational and leisure-time activities.

NSAID = nonsteroidal anti-inflammatory drug

Table 2.

Pack-years^a of Smoking and Risk of Moderate or Worse Hearing Loss in the Nurses' Health Study II, 1991-2013

Smoking	No. of Cases	Person-Years	Age-Adjusted RR (95% CI)	Multivariable-Adjusted RR ^b (95% CI)
Never Smoker	1681	1023115	1.00 (ref)	1.00 (ref)
Past Smoker				
1-9 pack-years	394	215127	1.08 (0.96, 1.20)	1.10 (0.98, 1.23)
10-19 pack-years	275	114712	1.33 (1.17, 1.51)	1.32 (1.16, 1.50)
20+ pack-years	144	48753	1.36 (1.14, 1.62)	1.30 (1.09, 1.55)
<i>p</i> -trend			<0.001	<0.001
Current Smoker				
1-9 pack-years	36	24127	1.12 (0.80, 1.56)	1.13 (0.80, 1.59)
10-19 pack-years	66	40439	1.15 (0.89, 1.47)	1.16 (0.90, 1.49)
20+ pack-years	164	66941	1.25 (1.06, 1.47)	1.21 (1.02, 1.43)
<i>p</i> -trend			0.003	0.02

^aNumber of pack-years = (number of packs smoked per day) x (number of years as a smoker)

^bAdjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity, intake of folate, magnesium, vitamin B12, vitamin C, beta-carotene, beta-cryptoxanthin, trans-fat, and long-chain omega-3 polyunsaturated fatty acid, history of hypertension, diabetes, tinnitus, NSAID use, and acetaminophen use.

RR = Relative Risk

CI = Confidence Interval

Table 3.

Time Since Smoking Cessation and Risk of Moderate or Worse Hearing Loss in the Nurses' Health Study II, 1991-2013

Time Since Smoking Cessation	No. of Cases	Person-Years	Age-Adjusted RR (95% CI)	Multivariable-Adjusted RR ^a (95% CI)	Multivariable-Adjusted RR ^b (95% CI)
<5 years	106	52535	1.42 (1.17, 1.74)	1.43 (1.17, 1.75)	1.30 (1.02, 1.66)
5-9 years	98	52638	1.27 (1.04, 1.57)	1.27 (1.03, 1.57)	1.16 (0.91, 1.48)
10-14 years	117	64633	1.16 (0.96, 1.41)	1.17 (0.96, 1.41)	1.08 (0.87, 1.35)
15-19 years	128	67218	1.12 (0.94, 1.35)	1.13 (0.94, 1.36)	1.06 (0.86, 1.30)
20+ years	364	139760	1.18 (1.05, 1.32)	1.18 (1.04, 1.32)	1.12 (0.98, 1.29)
Never Smoker	1681	1023115	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>p</i> -trend			<0.001	<0.001	0.06

^aAdjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity, intake of folate, magnesium, vitamin B12, vitamin C, beta-carotene, beta-cryptoxanthin, trans-fat, and long-chain omega-3 polyunsaturated fatty acid, history of hypertension, diabetes, tinnitus, NSAID use, and acetaminophen use.

^bAdjusted for all of the covariates above and pack-years of smoking

RR = Relative Risk

CI = Confidence Interval