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Does quitting smoking decrease the risk of midlife hot flashes? A longitudinal analysis

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ABSTRACT

Epidemiological studies have shown that cigarette smoking is associated with an increased risk of midlife hot flashes; however, the effect of quitting smoking on this risk is unclear. The purpose of this study was to examine the effect of quitting smoking on hot flashes using data from 761 women aged 45 to 54 years of age at baseline followed for 1 to 7 years. Results showed that women who quit smoking were less likely to suffer from hot flashes, less likely to have severe hot flashes, and less likely to have frequent hot flashes than women who continued to smoke (OR = 0.55, 0.80, 0.76), but were more likely to suffer from any hot flashes, more severe hot flashes, and more frequent hot flashes than women who never smoked (OR = 2.55, 1.68, 1.46). Subset analysis of the 353 women who had ever smoked found that women who had quit smoking for longer than 5 years had significantly lower odds, severity, and frequency of hot flashes than women who had continued smoking (OR = 0.36, 0.62, 0.63) or women who had quit in the previous 5 years (OR = 0.66, 0.77, 0.69). These findings suggest that that early smoking cessation programs may improve women's well-being during the menopausal transition.

1. Introduction

Approximately 75% of perimenopausal women will experience vasomotor symptoms, which include hot flashes [1]. The economic cost of hot flashes is significant, as experiencing this symptom can lead to medical treatment, physician visits, laboratory testing, and loss of productivity [2]. Women experiencing hot flashes also report a decrease in quality of life [3] and level of self-worth [4].

The risk and severity of hot flashes has been shown to vary with exercise [4], ethnicity [5], and body mass index (BMI) [6]. One factor that has consistently been shown to be associated with and increased risk of midlife hot flashes is history of cigarette smoking [5–12]. Cohort studies have found that current smokers had increased risk of hot flashes [5–7,12], severe hot flashes [7], and discomfort due to symptom [8]. A cross-sectional survey of perimenopausal women found that current smokers were at an increased risk for moderate to severe hot flashes and daily hot flashes, and that the risk for hot flashes increased with the amount smoked [10]. Similarly, a cross-sectional study of perimenopausal women found that current and former smokers, when compared to non-smokers, had higher odds of experiencing hot flashes and of severe hot flashes [11]. The mechanism by which smoking is associated with hot flashes is not clear, but several studies suggest that cigarette smoking may decrease levels of bioavailable estrogen [13–16] through increased hepatic metabolism [17], and low estrogen levels could explain the increased risk of hot flashes. However, the effect of quitting smoking on hot flashes has never been specifically studied, and no studies of former smokers have considered the amount of time since quitting. As quitting smoking is one of the personal modifications a woman can make to alter her health [18], it is important to precisely determine the benefit to be gained by quitting smoking.

Thus, the goal of this study was to explicitly calculate the effect of quitting smoking on the risk, severity, and frequency of hot flashes. Specifically, we established the time-dependent effect of quitting smoking on hot flashes, to determine the benefit associated with quitting over time.

2. Materials and methods

The study design for the parent study is described in detail elsewhere [6]. Briefly, a cohort study of hot flashes among women 45–54 years of age was conducted starting in 2006 among residents of Baltimore and its surrounding counties. Women were

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recruited by mail, and were included if they were in the target age range, had intact ovaries and uteri, and were pre- or perimenopausal. Exclusion criteria consisted of pregnancy, a history of cancer, exogenous female hormone or herbal/plant substance, and no menstrual periods within the past year. Participants made a baseline clinic visit, which included measurement of height and weight to calculate body mass index (BMI) and completion of a detailed 26-page baseline survey. Participants were asked to complete a brief questionnaire during a clinic visit 3 weeks after the baseline visit, then annually after that. This questionnaire repeated all previous questions about hot flashes and smoking, and BMI was calculated during the visit. Menopausal status was defined as follows: premenopausal women were those who experienced their last menstrual period within the past 3 months and reported 11 or more periods within the past year; perimenopausal women were those who experienced (1) their last menstrual period within the past year, but not within the past 3 months, or (2) their last menstrual period within the past 3 months and experienced 10 or fewer periods within the past year; postmenopausal women were those women who had not experienced a menstrual period within the past year. Follow-up was discontinued for women if they reported hormone therapy, an oophorectomy, or a cancer diagnosis. At the year 4 visit, follow-up was discontinued for women determined to be postmenopausal. This analysis included all participants enrolled as of February 2015, and consisted of the information gathered in the baseline survey and in the annual follow-up surveys.

For this analysis, history of hot flashes consisted of 3 variables collected in the survey. Participants were asked if they had, ever (at baseline) or in the last year (for follow-ups), had hot flashes (yes/no/don't know); the response to this was the dependent variable for a logistic regression analysis. Participants were also asked the severity of their hot flashes (none/mild/moderate/severe) and the frequency of their hot flashes (never/monthly/weekly/daily). These responses were dependent variables for separate ordinal logistic regression analyses. All variables related to the history of hot flashes were time varying; the variable "had a hot flash" related only to hot flashes previous to the survey date, and did not include future information about the development of hot flashes.

The full data set was used to analyze associations with the history of hot flashes using logistic regression. If the response to the survey question "Have you experienced hot flashes?" is defined as $\mathbf{Y}$, where the Y_i are independent Bernoulli random variables where 1 indicates the answer "yes", $E[Y_i] = \pi(\mathbf{X_i})$, $\mathrm{Var}(Y_i) = \pi(\mathbf{X_i})(1-\pi(\mathbf{X_i}))$, and $\mathbf{X_i}$ is the vector of explanatory variables for sample i, then

$$\pi(\mathbf{X_i}) = \frac{\exp\left(\beta'\mathbf{X_i} + \gamma z_i\right)}{1 + \exp\left(\beta'\mathbf{X_i} + \gamma z_i\right)} \quad (1)$$

where $\boldsymbol{\beta}$ is the vector of the effects of explanatory variables, z_i is the indicator of the individual, and γ is normally distributed with a mean of 0 and variance of σ^2_λ. A random effects model was used as results from the same individual were assumed to not be independent. Bivariate logistic regression was used to identify potential covariates for a multivariate logistic regression. For this logistic model, $\mathbf{X_i}$ initially contained the following variables: smoking history (never smoked, former smoker, current smoker), menopausal status (premenopausal, perimenopausal, or postmenopausal), education level (did not graduate college or graduated college), race (white or non-white), BMI, amount smoked ($\leq$25 packs/year or >25 packs/year), and type of cigarette smoked (filtered or unfiltered). Amount smoked was dichotomized, as the distribution of the continuous variable was highly skewed. Smoking history, menopausal status, and BMI were all time varying. The full model also considered interactions between BMI category and smoking history. Backwards model selection was performed using the likelihood ratio test, with factors maintained at a level of $\alpha = 0.1$. Confidence intervals (CI) were calculated using the likelihood profile method with a cutoff of 10^{-5}.

A subset of the data, consisting of all women self-reporting as current or former smokers, was used to analyze associations with the history of hot flashes given the years since quitting, where three different configurations of $\mathbf{X_i}$ were considered, all including the covariates listed above plus a term for years since quitting. This term was either: a linear term (years since quitting, with a value of 0 for current smokers), a large categorical variable {0, (0–5], (5–15], (15–25], >25}, and a reduced categorical variable {0, (0–5], >5}. Model selection proceeded as with the full data set logistic regression analysis above.

The severity and frequency of hot flashes were analyzed using ordinal logistic regression with a proportional odds model. In the case of severity, $\mathbf{Y}$ is defined as the response to the survey question "How severe are your hot flashes?", where 0 indicates "no hot flashes", 1 indicates "mild", 2 indicates "moderate", and 3 indicates "severe". In the case of frequency, $\mathbf{Y}$ is defined as the response to the survey question "How often do you experience hot flashes?", where 0 indicates "never", 1 indicates "monthly", 2 indicates "weekly", and 3 indicates "daily". In this model, $E[Y_{ik}] = \pi_k(\mathbf{X_i})$, $\mathrm{Var}(Y_{ik}) = \pi_k(\mathbf{X_i})(1-\pi(\mathbf{X_i}))$, $\mathbf{X_i}$ is the vector of explanatory variables for sample i, and

$$\pi_k(\mathbf{X_i}) = \frac{\exp\left(\beta'\mathbf{X_i} + \gamma z_i + \alpha_k\right)}{1 + \exp\left(\beta'\mathbf{X_i} + \gamma z_i + \alpha_k\right)} \quad (2)$$

where $\boldsymbol{\beta}$, z_i, and γ are as above, and α_k is the intercept for the kth level of $\mathbf{Y}$. Model selection proceeded as with the full data set logistic regression analysis above. This model was fit to all configurations of $\mathbf{X_i}$, with the full data set and with the subset as appropriate.

As baseline reporting of hot flashes differed from following years, sensitivity analyses were performed by omitting the baseline visit from each of the analyses. Model fitting proceeded as detailed above, and results were compared.

Logistic regression was performed using the glmer function of the lme4 package [19] and the proportional hazards model was fit using the ordLORgee function of the multgee package [20]. Models were fit with individual as a random effect to account for within-woman correlation. Proportional odds assumptions were tested by visualization of the empirical cumulative logit function. All analyses were performed in R, using the Revolution R Enterprise system [21].

3. Results

3.1. Description of data

There were 2275 observations of 761 women over a 7 year period, with the number of observations per woman varying from 1 to 7. Table 1 shows the baseline characteristics of the women in the study and their association with hot flashes. Compared to women not experiencing hot flashes, women experiencing hot flashes were more likely to have not graduated from college, to be non-white, and to have a BMI of $\geq$30. Women experiencing hot flashes were also more likely to be a current or former smoker than women not experiencing hot flashes.

Table 2 shows the distribution of hot flash severity and frequency by smoking history. Fifteen women quit smoking during the study, and this change in status was included in the analysis. A higher proportion of current and former smokers experienced moderate and severe hot flashes. Monthly hot flashes were the most common in all groups, but current and former smokers were numerically more likely than non-smokers to have hot flashes at