Use of Mentholated Cigarettes and Lung Cancer Risk[1]

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ABSTRACT

Black males have higher age-adjusted lung cancer incidence rates compared to white males, and blacks of both sexes have higher rates of increase in lung cancer incidence over past decades. The majority of black smokers smoke mentholated cigarettes. These observations prompted us to assess the effect of smoking mentholated cigarettes on lung cancer risk, using data from a hospital-based case-control study of tobacco-related cancers. Analysis was restricted to current cigarette smokers and was carried out on 588 male lung cancer cases and 914 male control patients and on 456 female lung cancer cases and 410 female controls interviewed between 1985 and 1990. The prevalence of menthol usage did not differ between cases and controls of either sex. No significant association was observed between either short-term (1–14 years) or long-term (15+ years) menthol use and lung cancer in logistic regression analyses adjusting for covariates. For specific histological types of lung cancer there was no indication of an association with menthol usage.

INTRODUCTION

Black American males have higher (by approximately 50%) age-adjusted lung cancer incidence rates compared to white males (1), and the rate of increase in lung cancer incidence over the past five decades has been greater in blacks of both sexes than in whites (1–4). The reason for these black-white differences is unknown. Blacks tend to smoke mentholated cigarettes and cigarettes which are higher in tar and nicotine compared to whites (5–7). It has been suggested that the use of mentholated cigarettes could explain some of the higher chronic disease, including lung cancer, mortality in blacks (7). No epidemiological study has examined whether the use of mentholated cigarettes carries a higher risk of lung cancer relative to the use of nonmentholated cigarettes, although we have previously investigated a possible association with esophageal cancer (8). We report here the results of such a study in relation to cancer of the lung.

MATERIALS AND METHODS

Data used in this analysis derive from a case-control study of tobacco-related cancers which has been described previously (9). In the original study, for each case of a tobacco-related cancer one matched control patient was sought and interviewed within 2 months of the case's interview. Subjects were interviewed in 8 hospitals in four United States cities (New York, Chicago, Philadelphia, and Detroit). Controls were matched to cases on: age (±5 years), sex, race (black, white, Hispanic), hospital, and date of interview. Controls were hospitalized patients with conditions thought not to be associated with smoking, including: cancers (of the colon, stomach, female breast, prostate, and skin, as well as leukemia, lymphoma, sarcomas, etc.); benign neoplastic diseases; and nonneoplastic conditions (such as musculoskeletal and connective tissue disorders, eye conditions, injuries, etc.).

For the purposes of the present analysis only current smokers of cigarettes (defined as subjects who had smoked within the year preceding diagnosis) were included. We selected all available lung cancer cases and all controls who were current smokers. A total of 588 male and 456 female cases and 914 male and 410 female controls, interviewed between 1985 and 1990, were available for analysis.

All patients were interviewed in the hospital by trained interviewers using a standard questionnaire. This contained questions on the type of tobacco products used throughout life (cigarettes, cigars, pipes, chewing tobacco, snuff), brands of cigarettes smoked (up to seven brands per person), CPD,[3] use of filter and nonfilter cigarettes, use of mentholated cigarettes, years of smoking each brand, and age at initiation of smoking. Fewer than 1% of subjects reported 7 or more cigarette brands (97% reported 5 brands or fewer). If a subject reported smoking 2 different brands concurrently, both were recorded, but the duration was counted only once in computing the total duration. If a subject was unable to recall a brand name, the amount, duration, and mentholation status of the cigarette was recorded. In addition, information was obtained on sociodemographic factors, including age, years of education, and occupational level. Data on weight 5 years prior to diagnosis and height were collected and used to compute BMI for each subject.

Information on mentholation was obtained for each brand of cigarette reported. Among mentholated cigarette smokers, the most commonly reported brands (for the brand currently smoked) were Salems (28%) and Kools (21%). Only 2% of male subjects (cases and controls) and 5% of female subjects had used mentholated cigarettes exclusively, whereas 24% of male and female subjects had smoked both mentholated and nonmentholated brands. For this reason we classified subjects into those who had never smoked a mentholated brand or had smoked one for less than 1 year ("nonmenthol smokers"), those who had smoked a mentholated brand for between 1 and 14 years, and those who had smoked a mentholated brand for 15 years or more.

The effect of smoking mentholated cigarettes was assessed in all lung cancer cases combined as well as in four specific histological types of lung cancer (squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenocarcinoma) and controls.

Unconditional logistic regression was used to determine the effect of menthol use on lung cancer and on specific histological types with adjustment for covariates including CPD (of the current brand), duration of smoking, inhalation, race, education, age, and BMI. CPD, years of smoking, years of education, and age were entered as continuous variables. The remaining variables were categorized as follows: mentholated cigarette exposure (never, 1–14 years, 15+ years), race (white, black; 14 subjects who were Hispanic were excluded from these analyses), inhalation (deeply *versus* not at all, slightly, moderately), BMI (≥ 28, <28). BMI of ≥ 28 corresponds to the highest quartile and is consistent with the conventional definition of overweight (10). Additionally, we modeled the relationship between lung cancer and these covariates by fitting both duration of menthol and duration of nonmenthol smoking as continuous terms in the model, thus eliminating the categorical terms for menthol exposure. In this analysis we were able to examine the effects of both menthol and nonmenthol smoking independently.

For cell type-specific analyses, males and females were combined due to small numbers and sex was included in the model as an independent variable. Potential interactions between menthol use (ever,

never) and other variables were evaluated and three interaction terms were included in the logistic regression model: menthol*age; menthol*education; and menthol*BMI.

RESULTS

Table 1 gives the distribution of selected sociodemographic and behavioral factors among cases and controls by sex. Cases were slightly older than controls. Mean age (years) was 57.4 for male cases, 55.1 for male controls, 57.9 for female cases, and 56.3 for female controls. Cases and controls had similar distributions by race, year of education, and occupational level. Only 8 subjects were classified as other than black or white (6 male cases and 7 male controls were Hispanic; 1 female case was Hispanic). As expected, cases reported smoking more cigarettes per day and longer duration of smoking, as well as deeper inhalation compared to controls. In males, menthol usage [categorized as never smoked mentholated brand; smoked mentholated brand(s) between 1 and 14 years; smoked mentholated brand(s) for 15 or more years] was virtually identical between cases and controls; in females, smaller proportions of cases reported ever smoking mentholated brands compared to controls.

The prevalence of menthol use among controls in the present study, by race and sex, is compared with that in two other surveys in Table 2. Age-specific prevalence is given for the present study and the Adult Use of Tobacco Survey data (11), and age-adjusted prevalence is presented for the data of Sidney *et al.* (7). The prevalence by sex and race is generally similar in the three surveys. Use of mentholated cigarettes was more common in females, and in both sexes blacks had roughly twice the prevalence of whites.

Logistic regression results for lung cancer stratified by sex are presented in Table 3. Among smoking variables, CPD and duration of smoking were significantly associated with lung cancer in both sexes. Use of mentholated cigarettes for either 1–14 years or 15+ years was not associated with increased risk. Being overweight (BMI ≥28) was associated with significantly reduced risk in both sexes. Inhalation (deeply *versus* not at all, slightly, moderately) showed a significant positive association in females only. The inclusion of interaction terms for menthol*education and menthol*BMI, both of which were statistically significant in both sexes, did not alter the β coefficients for mentholated cigarette use and reduced but did not eliminate the significant main effect of BMI (data not presented).

In the model containing years of menthol cigarette use and years of nonmentholated cigarette use (both as continuous variables), the β coefficients for years of menthol were smaller than those for years of nonmenthol in both sexes.

In cell type-specific logistic regression analyses, neither short-term (1–14 years) nor long-term (15+ years) user of mentholated cigarettes was associated with squamous cell, small cell, large cell, or adenocarcinoma of the lung (Table 4). Additionally, there was no suggestion of a trend in risk with increasing duration of exposure. In contrast, CPD and duration of smoking showed statistically significant associations with each of the four types.

DISCUSSION

We investigated the use of mentholated cigarettes as a potential risk factor for lung cancer, because blacks use these cigarettes to a greater extent than whites, and black males have

Table 1 *Distribution (%) of demographic and behavioral factors in lung cancer cases and controls (all current smokers)*

	Males (%)		Females (%)	
	Cases (N = 588)	Controls (N = 914)	Cases (N = 456)	Controls (N = 410)
Age				
<50	20.1	29.3	19.5	23.4
50–59	37.1	32.9	36.0	37.1
60–69	33.8	31.1	32.9	30.5
70+	9.0	6.7	11.6	9.0
Education				
≤12 yr	56.3	59.0	68.1	62.4
13–15 yr	21.9	20.8	18.9	22.7
16+ yr	21.8	20.2	13.0	14.9
Race				
White	85.4	85.2	87.3	82.7
Black	13.6	14.0	12.5	17.3
Other[a]	1.0	0.8	0.2	0.0
Occupational level				
Professional/managerial	27.9	26.0	12.3	16.8
Skilled	46.8	47.0	48.7	46.1
Semiskilled	16.8	17.6	7.4	7.8
Unskilled	8.5	9.4	9.2	10.0
Housewife			22.4	19.3
Menthol				
Never	74.9	73.3	75.8	64.9
1–14 yr	13.1	13.1	11.3	17.2
15+ yr	12.0	13.6	12.9	19.9
CPD				
1–20	37.9	56.0	48.0	70.7
21–30	16.5	17.5	22.4	16.1
31–40	26.2	17.2	22.4	9.0
41+	19.4	9.3	7.2	4.2
Inhalation				
Not at all, slightly, moderately	62.1	69.4	69.3	86.8
Deeply	37.9	30.6	30.7	13.2
Duration of smoking				
≤30 yr	17.4	29.8	18.0	32.7
31–40 yr	32.6	31.5	36.8	37.5
41+ yr	50.0	38.7	45.2	29.8
Body mass index				
<28	78.5	72.3	86.7	77.8
≥28	21.5	27.7	13.3	22.2

[a] Among males, 6 cases and 7 controls were Hispanic. Among females, 1 case was Hispanic.

higher lung cancer incidence rates compared to whites. Existing data on the carcinogenicity of the combustion products of menthol (12–14), while sparse, lend support to the hypothesis that use of mentholated cigarettes could increase the risk of lung cancer over that of smokers of nonmentholated cigarettes.

Use of mentholated cigarettes was not associated with increased risk of lung cancer or of specific histological types of lung cancer in this study. In contrast, the number of cigarettes smoked per day and duration of smoking were strong risk factors. BMI showed an inverse association with lung cancer. This last finding will be the subject of a separate paper.

Classification of smokers into users of mentholated and nonmentholated brands was made possible by questions which elicited for each cigarette brand whether it was menthol or nonmenthol. The prevalence of smoking mentholated cigarettes among current smokers by race and sex in this study was comparable to that reported in other surveys.

Only 2.2% of male subjects had smoked mentholated cigarettes exclusively, whereas 74.3% had smoked nonmentholated brands exclusively, and 23.5% had smoked mixed mentholated and nonmentholated brands. Among female subjects, the cor-

Table 2 *Prevalence (%) of smoking metholated cigarettes among current smokers by race and sex in the study population and in United States surveys*

| | Whites | | | | | Blacks | | | | |
| | AHF[a] age group | | AUTS age group | | | AHF age group | | AUTS age group | | |
	45–64 yr	65+ yr	45–64 yr	65+ yr	Sidney[b]	45–64 yr	65+ yr	45–64 yr	65+ yr	Sidney
Males										
Total N	505	149	537	167	7352	75	27	58	[c]	4294
% menthol	18.0	15.4	14.3	14.4	18.1	34.7	44.4	45.1		49.9
Females										
Total N	223	73	570	222	8843	47	15	69	[c]	6459
% menthol	22.9	24.7	25.5	21.8	27.1	48.9	46.7	69.1		55.5

[a] AHF, prevalence in controls in the present (American Health Foundation) study; AUTS, data from Adult Use of Tobacco Survey, 1986 (11).
[b] Data from Sidney *et al.* (7) are age-adjusted by the direct method, with the age distribution of the entire study population used as the standard.
[c] Numbers are too small to permit stable estimates.

Table 3 *Adjusted OR[a] for lung cancer due to menthol and other factors among current smokers, 1985–1990*

| | Males | | Females | |
	OR	95% CI	OR	95% CI
Categorical variables[b]				
Menthol 1–14 yr	1.14	0.82–1.59	0.82	0.52–1.28
Menthol 15+ yr	0.98	0.70–1.38	0.76	0.53–1.16
Inhalation	1.07	0.84–1.36	2.03	1.38–2.98[c]
Race	1.47	1.05–2.06	1.05	0.68–1.64
BMI	0.64	0.49–0.83[c]	0.47	0.32–0.70[c]
Continuous variables (integer values)				
Age	0.97	0.94–1.00	0.96	0.93–0.99
Education	0.72	0.57–0.91	1.37	1.00–1.88
CPD	1.03	1.02–1.04[c]	1.04	1.02–1.05[c]
Duration of smoking	1.07	1.04–1.09[c]	1.08	1.06–1.11[c]

[a] OR, odds ratio; CI, confidence interval.
[b] Categorized as: menthol 1–14 years or 15+ years *versus* never menthol; inhalation (deeply *versus* not at all, slightly, moderately); race (black *versus* white); BMI (≥28 *versus* <28).
[c] $P < 0.001$; for continuous variables, p refers to the test for linear trend.

Table 4 *Adjusted[a] odds ratios for specific histological types of lung cancer due to menthol among current smokers (males and females combined)*

Histological type	OR	95% CI
Squamous cell carcinoma (N = 268)		
Menthol 1–14 yr	1.17	0.78–1.78
Menthol 15+ yr	0.92	0.60–1.42
Small cell carcinoma (N = 131)		
Menthol 1–14 yr	0.80	0.43–1.48
Menthol 15+ yr	0.86	0.49–1.51
Large cell carcinoma (N = 106)		
Menthol 1–14 yr	1.99	0.73–5.41
Menthol 15+ yr	0.84	0.27–2.61
Adenocarcinoma (N = 400)		
Menthol 1–14 yr	0.98	0.68–1.42
Menthol 15+ yr	0.95	0.66–1.36

[a] Adjusted for the following variables in logistic regression models: sex (male *versus* female), age (continuous), CPD (continuous), duration of smoking (continuous), race (black *versus* white), years of education (continuous), inhalation (deeply *versus* not at all, slightly, moderately), BMI (≥28 *versus* <28).

responding percentages were 4.6, 71.7, and 23.7%. Furthermore, among "mixed smokers," the mean years of smoking mentholated cigarettes were approximately 15 years out of 37 years total duration of smoking. In addition, because use of mentholated cigarettes has been widespread only since the 1960s, it may be too early to assess their full impact on lung cancer risk. Nevertheless, the failure to detect any suggestion of increased risk among users of mentholated cigarettes indicates that menthol smoking is not a strong risk factor for lung cancer.

Use of mentholated cigarettes could contribute indirectly to increased lung cancer risk if smokers of mentholated cigarettes tended to inhale to a greater extent than smokers of nonmentholated brands, as has been proposed (6, 7, 15, 16), or if menthol smokers increased their exposure to tobacco smoke carcinogens by other means. Our data (17) and those of others (7, 16) suggest that menthol smokers do not inhale more than nonmenthol smokers. However, as pointed out by Sidney *et al.* (7), reporting of inhalation could be biased by menthol status, since menthol has anesthetic properties.

If our results are confirmed by other researchers, the implication would be that use of mentholated cigarettes does not explain black-white differences in lung cancer incidence rates or time trends. Other hypotheses need to be formulated to explain these differences.

ACKNOWLEDGMENTS

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