

Original Contributions

CIGARETTE SMOKING, RELATIVE WEIGHT, AND MENOPAUSE

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To examine the interrelationships of cigarette smoking, relative weight, and the occurrence of natural menopause, the authors prospectively evaluated the experience of 66,663 female US registered nurses who were premenopausal in 1976. Over a two-year period, 5004 women became post-menopausal. Current smokers were more likely than past or never smokers to develop menopause, although the effects of smoking diminished with age. The rate ratios of menopause for current smokers vs. never smokers (with 95% confidence limits) for women aged 30-39, 40-44, 45-49, and 50-55 years were 1.90 (1.10-3.28), 2.16 (1.73-2.69), 1.53 (1.41-1.67), and 1.20 (1.12-1.28). These rate ratios were not appreciably affected by adjustment for relative weight. Median ages at menopause were 52.4 for never smokers and 51.9, 51.0, 50.7, and 50.4 years for women who currently smoked 1-14, 15-24, 25-34, and 35 or more cigarettes per day. A crude linear relationship between relative weight and occurrence of menopause was observed. Comparing the leanest and heaviest quintiles, rate ratios for menopause among women aged 30-39, 40-44, 45-49, and 50-55 years were 1.42 (0.74-2.75), 1.26 (0.95-1.69), 1.25 (1.13-1.41) and 1.08 (0.99-1.19). The effect of relative weight was in part explained by the tendency of current smokers to weigh less than nonsmokers. After adjustment for current cigarette consumption a weak linear relationship between relative weight and menopause remained among women who smoked, although no such association was seen among nonsmokers.

menopause; obesity; smoking

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In several case-control studies, cigarette smoking (1-4) and lean body build (5, 6) have been found to predict early menopause. Whether both cigarette smoking and premenopausal weight are independent determinants of menopause has not been fully assessed. Smokers generally are thinner than nonsmokers (7), and it is not clear whether they have an earlier menopause because they are relatively lean or because they smoke. The importance of identifying factors related to menopause extends beyond this immediate event since such factors are also likely to be related to the incidence of hormonally dependent tumors such as breast cancer, which is known to be associated with age at menopause.

Previous studies have generally utilized data on smoking and body build collected some years after menopause, raising the question whether the event altered smoking behavior and anthropometric variables or their recall. The collection of information on smoking, weight, height, and menopausal status for a large group of women in 1976 and again in 1978 afforded the opportunity to examine the interrelationships of these variables in prospective data.

MATERIALS AND METHODS

All married, female registered nurses aged 30-55 years in 1976 and residing in 11 of the larger states of the United States were identified from a computer tape provided by State Boards of Nursing and the American Nurses' Association. In 1976, these women were mailed questionnaires requesting information on various health related items including whether or not their menstrual periods had ceased permanently. The overall study has been described elsewhere (8).

Of the 121,964 women who completed the questionnaire, 78,678 indicated that their menstrual periods had not ceased permanently. Of those women who were initially premenopausal, 69,906 (89 per

cent) responded to a two-year follow-up questionnaire in 1978. At that time, we again inquired whether a woman's menstrual periods had permanently ceased and a positive response was defined as an incident menopause. Smoking status was determined by responses to the 1976 questionnaire. Women were classified as current, past, or never smokers as of that time and were further categorized by number of cigarettes smoked per day and age of starting. A relative weight score was determined from weights and heights reported in 1976 by ranking women according to weight for each inch of height and year of age. Every woman was assigned a percentile score within each height and age category.

Among respondents to the 1978 questionnaire, 2864 reported a surgical menopause, 23 were postmenopausal due to radiation therapy, and 356 did not report their current menopausal status. The remaining 66,663 women who were premenopausal in 1976 and who completed the 1978 questionnaire are the basis of the present analysis.

Two-year cumulative incidence rates of menopause were computed for exposure categories. To assess the relationships of exposure with menopause, we calculated rate ratios with 95 per cent confidence limits (9) and rate differences (attributable risks). Chi-square tests for trend, with and without the Mantel extension for stratified data (10), were used to assess the effect of increasing levels of smoking and relative weight. Rate ratios within categories of potential confounding variables were summarized using a maximum likelihood method (10) or direct standardization. Life table analysis was used to determine median age at menopause, and multiple logistic regression (11) was employed to examine the simultaneous effects of several variables on rates of menopause. Since few younger women ceased menstruating during two years of follow-up and the overall effects

of smoking and obesity were minimal among women over 50 years of age, a number of detailed analyses were restricted to women 40-49 years old. When data were incomplete for one or more variables, the total number of women in the tables is slightly less than 66,663.

RESULTS

During the two years of follow-up, 5004 (7.5 per cent) of the 66,663 premenopausal women became postmenopausal, and current smokers were more likely to cease menstruating than those who had never smoked (table 1). Although the effect of smoking, as indicated by rate ratios, diminished with age (table 1), rate differences for current smokers vs. never smokers increased markedly with age because age itself is the strongest determinant of menopause (figure 1). Median ages at menopause derived from life table analyses were 52.4 years for never smokers and 51.9, 51.0, 50.7, and 50.4 years, respectively, for women smoking 1-14, 15-24, 25-34, and 35 or more cigarettes per day.

As in previous studies, current smokers tended to be leaner than those who had

stopped or never smoked. For example, 23.1 per cent of current smokers were in the lowest quintile of relative weight in contrast to 18.1 per cent of never smokers and 17.3 per cent of ex-smokers. To determine whether smoking was independently related to incidence of menopause, we examined this relationship within each quintile of relative weight. Within each level of relative weight, current smokers were more likely to cease menstruating than never smokers, and the summary rate ratios adjusted for relative weight were all close to the crude values (table 1). Among current smokers aged 40-49 years, for whom there was a substantial overall relationship between smoking and menopause incidence, the incidence of menopause was strongly related to the number of cigarettes smoked daily (figure 2).

The probability of menopause among ex-smokers was, overall, only slightly greater than among never smokers and this increase was not statistically significant except in women 40-44 years of age. To determine whether women who recently stopped smoking experienced a residual effect from the previous use of ciga-

TABLE 1
Two-year age-specific incidence of menopause by smoking status among a sample of female US nurses initially surveyed in 1976

Age (years)	Smoking status	Total women	Incident menopause	Rate ratios (95% confidence limits)	
				Crude	Adjusted*
30-39	Current smoker	10,717	29	1.90 (1.10, 3.28)	1.87 (1.09, 3.23)
	Ex-smoker	7877	12	1.07 (0.53, 2.16)	1.08 (0.54, 2.18)
	Never smoker	15,477	22	1.00†	1.00†
40-44	Current smoker	5214	194	2.16 (1.73, 2.69)	2.13 (1.71, 2.66)
	Ex-smoker	3968	91	1.33 (1.02, 1.74)	1.33 (1.02, 1.75)
	Never smoker	6788	117	1.00†	1.00†
45-49	Current smoker	3681	869	1.53 (1.41, 1.67)	1.49 (1.36, 1.62)
	Ex-smoker	3019	479	1.03 (0.93, 1.14)	1.03 (0.93, 1.14)
	Never smoker	5083	782	1.00†	1.00†
50-55	Current smoker	1161	679	1.20 (1.12, 1.28)	1.19 (1.12, 1.28)
	Ex-smoker	1170	597	1.04 (0.97, 1.12)	1.04 (0.97, 1.12)
	Never smoker	2276	1112	1.00†	1.00†

* Maximum likelihood summaries of rate ratios from data stratified by categories of relative weight.

† Reference categories.

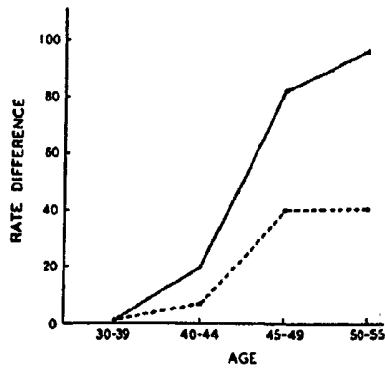


FIGURE 1. Differences in rates of menopause among a sample of female US nurses. Current smokers vs. never smokers are indicated by the solid line and lowest relative weight quintile vs. heaviest relative weight quintile by the interrupted line. Rates are crude two-year cumulative incidence rates per 1000 women.

rettes, we examined the probability of menopause among ex-smokers 40-49 years of age according to the number of years since they had stopped smoking. Individuals who have recently stopped

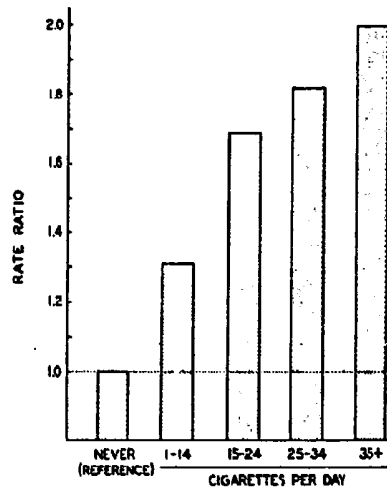


FIGURE 2. Rate ratios for menopause by number of cigarettes smoked per day among a sample of female US nurses who were aged 40-49 years in 1976. χ^2 trend, Mantel extension = 23.8, $p < 0.001$.

smoking have a high probability of starting to smoke again, and an apparent residual effect of smoking could actually be due to the resumption of smoking. To minimize such a spurious effect, we restricted this analysis to ex-smokers in 1976 who continued to be ex-smokers on the two-year follow-up questionnaire (table 2). Women who had recently stopped smoking were found to have an elevated probability of menopause, although still somewhat lower than the rate among current smokers (χ^2 trend, Mantel extension = 3.88, $p < 0.05$). The age of starting to smoke had no material relationship with probability of menopause when adjusted for number of cigarettes currently smoked (χ^2 trend, Mantel extension = 0.32).

Women in the lowest quintile of relative weight were more likely to become postmenopausal than those in the highest quintile (table 3). As with smoking, the rate ratio tended to approach unity with increasing age, although rate differences markedly increased (figure 2). To determine the effect of smoking on the relationship between relative weight and menopause, this relationship was examined among categories of smoking (never smoker, ex-smoker, 1-14, 15-24, 25-34, and 35+ cigarettes per day). The summary rate ratios adjusted for smoking were somewhat closer to one than the unadjusted values, indicating that smoking explains some, but not all the association with relative weight. Among smokers aged 40-49 years, the incidence of menopause decreased regularly with increasing relative weight, while among women who never smoked, no such gradient was observed (table 4). Even when the extreme tenth and fifth percentiles of relative weight were examined among never smokers, there was no evidence of an increased rate of menopause among the leanest women.

We also considered the possibility that the relationships between smoking or rel-

TABLE 2

Relationship between the number of years since last smoked among ex-smokers and the incidence of menopause among a sample of female US nurses who were aged 40-49 years in 1976 and who were also nonsmokers in 1978

Age (years)		Never smoked	Years since last smoked				
			15+	10-14	5-9	2-4	<2
40-44	Total women	6740	930	1015	958	440	293
	Incident menopause	114	22	20	16	13	12
45-49	Total women	5042	1006	725	663	255	190
	Incident menopause	777	152	102	112	40	37
Age-standardized rate ratios*		1.00	1.03	0.95	1.08	1.11	1.41

Mantel extension chi-square test for trend among ex-smokers = 3.88, $p < 0.05$.

* Rate ratios are directly standardized using the age distribution for never smokers.

ative weight and menopause might be spurious because these exposures were associated with other determinants of menopause. Neither age at menarche, height, nor history of hypertension or diabetes were associated with age-specific rates of menopause. Although the rate of menopause was higher in nulliparous than in parous women, nulliparity was not materially associated with smoking or obesity, so that adjustment for its effect did not affect the other associations. The independent effects of current smoking, number of cigarettes smoked daily, relative weight (in quintiles) and nulliparity were confirmed in a multiple logistic re-

gression analysis (table 5). A cross-product term representing the interaction between current smoking and relative weight did not attain statistical significance when added to the model.

DISCUSSION

In these data, both cigarette smoking and low relative weight are independently associated with higher rates of menopause. However, the effect of relative weight is essentially limited to smokers, so that at all ages lean smokers experience the highest rate of menopause. The effects of both smoking and relative weight as estimated by rate ratios di-

TABLE 3

Two-year incidence of menopause by extreme quintiles of relative weight among a sample of female US nurses initially sampled in 1976

Age (years)	Weight quintile	Total women	Incident menopause	Rate ratios (95% confidence limits)	
				Crude	Adjusted*
30-39	Lean	6543	21	1.00†	1.00†
	Heavy	6653	15	0.70 (0.36, 1.36)	0.71 (0.36, 1.37)
40-44	Lean	3159	101	1.00†	1.00†
	Heavy	3085	78	0.79 (0.59, 1.06)	0.88 (0.65, 1.18)
45-49	Lean	2338	461	1.00†	1.00†
	Heavy	2331	367	0.80 (0.71, 0.99)	0.85 (0.75, 0.97)
50-55	Lean	803	427	1.00†	1.00†
	Heavy	958	470	0.92 (0.84, 1.01)	0.94 (0.85, 1.03)

* Maximum likelihood summaries of rate ratios adjusted for categories of smoking (never smoker, past smoker, and 1-14, 15-24, 35+ cigarettes per day).

† Reference category.

TABLE 4

Rate ratios for menopause by quintile of relative weight among a sample of currently and never smoking female US nurses aged 40-49 years in 1976

	Quintile of relative weight					Chi-squared trend, Mantel extension	p-value
	1	2	3	4	5		
Mean height (in.) ^a	64.5	64.8	64.5	64.5	64.5		
Mean weight (lbs.) ^a	116.7	127.9	136.8	148.7	161.7		
	Rate ratios [†]						
Current smokers	1.00 [‡]	1.03	0.90	0.80	0.75	18.1	<0.001
Never smokers	1.00 [‡]	0.88	0.96	0.88	0.89	1.17	0.3

^a 1 in. = 0.0254 m.; 1 lb. = 0.454 kg.

[†] Rate ratios are directly standardized for age (40-44, 45-49 years) and, among smokers, for numbers of cigarettes smoked daily (1-14, 15-24, 25-34, 35+).

[‡] Reference category.

minish with increasing age. This observation is compatible with the knowledge that inherent biologic determinants of menopause become relatively more important at older ages. However, the absolute effects of smoking and relative weight as measured by rate difference, which may better reflect the overall public health implications of these exposures, actually increase with advancing age.

The relationship between smoking and occurrence of menopause in this prospective follow-up study has been noted in most previous case-control studies (1-4), although not all (12). However, these studies were not consistently able to de-

tect a dose-response relationship between the number of cigarettes smoked per day and probability of menopause.

In contrast to smoking, the effect of relative weight observed in our data was weak and partly explained by the tendency of smokers to have a lower relative weight than nonsmokers. In cross-sectional data from the US National Health Examination Survey, MacMahon and Worcester (5) noted that thicker triceps skin folds were associated with a later age at menopause, but they provided no information on smoking. Sherman et al. (6) reported that, for women under age 50 years, those having an early

TABLE 5

Multiple logistic regression analysis of menopausal determinants among a sample of female US nurses aged 40-49 years in 1976

Variables ^a	Regression coefficient (± standard error)		Rate ratio (95% confidence limits) ^b
Constant	-22.771	(±0.449)	
Age	0.449	(±0.010) [†]	
Current smoking	0.610	(±0.052) [†]	1.84 (1.66, 2.04)
Ex-smoking	0.095	(±0.059) [†]	1.10 (0.98, 1.23)
Quantity smoked	0.18	(±0.037) [†]	
Relative weight	-0.052	(±0.016) [†]	
Nulliparity	0.377	(±0.076) [†]	1.46 (1.26, 1.69)

^a Categories of variables are: age—40, 41, . . . , 49 years; current smoking—no = 0, yes = 1; ex-smoking—no = 0, yes = 1; quantity smoked—1-14 cigarettes daily = 1, 15-24 = 2, 25-34 = 3, 35+ = 4 (the weighted average for these categories of quantity smoked was 2.1 so that deviations from this can be used to modify the overall effect of current smoking); relative weight—leanest quintile = 1, . . . , heaviest quintile = 5; nulliparity—parous = 0, nulliparous = 1.

[†] $p \leq 0.001$.

^b For dichotomous variables only, estimated as odds ratios from exponentiated regression coefficients.

menopause tended to have been leaner at age 18 years. Again, cigarette smoking was not considered in the analysis. Although the women in our study exhibited considerable variation in weight (table 4), it is possible that a stronger effect of relative weight might be observed among women with more extreme degrees of leanness than are found in a general US population. A greater real effect of relative weight could also have been reduced if the self-reporting of weight and height were inaccurate, resulting in misclassification of exposure. However, we actually weighed (using a digital bathroom scale) 184 study participants living in the greater Boston area 6-12 months after they completed the self-administered questionnaire. Although the measured weights averaged 1.5 kg (3.3 lbs) higher than the self-reported weights, these weights were highly correlated ($r = 0.96$).

Since menopause does not have a specific date of onset or diagnosis and women in this study were asked to determine themselves whether their menstrual periods had ceased, it is possible that lack of a stronger association with relative weight could result from misclassification if a substantial number of women who reported permanent cessation of their menstrual periods had not really stopped menstruating. To examine this possibility, we analyzed the responses of 608 women who first reported the permanent cessation of menstrual periods in 1978 and we compared their responses then to those they gave to the same question regarding cessation of menstrual periods on a second follow-up questionnaire in 1980. A total of 595 (98 per cent) of these women remained postmenopausal after an additional two years, substantiating the accuracy of their original report.

The mechanism by which smoking is related to earlier menopause has not been established. Aromatic hydrocarbons contained in cigarette smoke may destroy

primordial oocytes and thus hasten the onset of menopause (13). Our finding of a residual effect of smoking among women who recently stopped is compatible with this hypothesis. However, smoking may accelerate ovarian involution and aging in general, perhaps as a result of increased oxidation of cell membranes caused by combustion products such as nitrogen dioxide (14).

The consistency of our prospective findings with previous studies of menopause, the presence of dose-response relationships, and the failure to explain these observations on the basis of other potentially confounding variables all suggest that the associations of both cigarette smoking and relative weight with menopause are causal. Further support for the causal nature of these relationships may come from studies of the biologic mechanisms whereby smoking and relative weight are associated with menopause, particularly those which examine the relationships between smoking and levels of estrogen and gonadotropins.

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