

Cigarette Smoking and the Risk of Diabetes in Women

ABSTRACT

Objectives. Noninsulin-dependent diabetes mellitus, a major risk factor for cardiovascular disease, is prevalent in more than 12 million Americans. A voluminous amount of data demonstrates that cigarette smoking is an important cause of cancer and coronary heart disease. However, the association between cigarette smoking and the risk of diabetes is virtually unexplored, especially in women.

Methods. We examined the association between smoking and the incidence of noninsulin-dependent diabetes mellitus among 114 247 female nurses who were free of diabetes, cardiovascular disease, and cancer in 1976. We collected exposure information and disease status prospectively for 12 years from biennially self-administered questionnaires.

Results. Current smokers had an increased risk of diabetes, and we observed a significant dose-response trend for higher risk among heavier smokers. During 1 277 589 person-years of follow-up, 2333 women were clinically diagnosed with diabetes. The relative risk of diabetes, adjusted for obesity and other risk factors, was 1.42 among women who smoked 25 or more cigarettes per day compared with nonsmokers.

Conclusions. These data suggest that cigarette smoking may be an independent, modifiable risk factor for noninsulin-dependent diabetes mellitus. (*Am J Public Health.* 1993;83:211-214)

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Introduction

Cigarette smoking decreases fasting insulin levels and causes a transient increase in blood glucose levels after an oral glucose challenge.^{1,2} Cigarette smoking is also associated with a greater waist-to-hip ratio,^{3,4} a measure of fat distribution that is related to diabetes.^{5,6} However, the epidemiological data relating smoking to the development of diabetes are limited. In a 25-year prospective study among 841 middle-aged Dutch men,⁷ controlled for age, subscapular skinfold, resting heart rate, alcohol, and energy intake, the relative risk (RR) of diabetes was 3.3 (95% confidence interval [CI] = 1.4, 7.9) among men smoking more than 20 cigarettes per day compared with never smokers. However, control for relative weight, family history of diabetes, and physical activity was not complete. In two other relatively small studies, no relation was seen between smoking and diabetes.^{8,9} To determine whether an association between smoking and noninsulin-dependent diabetes mellitus exists in women after controlling for known risk factors, we examined this relationship prospectively among 114 247 participants in the Nurses' Health Study.

Methods

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses, aged 30 to 55 years and living in 11 US states, returned a mailed questionnaire. Every 2 years, participants are mailed follow-up questionnaires to update information on cigarette smoking and other risk factors and to ascertain newly diagnosed diseases. In 1980, we collected data on physical activity and alcohol consumption.¹⁰

Among the 121 700 women originally enrolled in this study, 114 247 were free from diabetes, coronary heart disease, and cancer in 1976. We mailed a supplementary questionnaire to women who reported a diagnosis of diabetes mellitus on any follow-up questionnaire. We defined cases of diabetes as being confirmed if one of the following conditions was reported on the supplementary questionnaire: (1) one or more classic symptoms (thirst, polyuria, weight loss, hunger, pruritus) plus an elevated fasting (≥ 140 mg/dL) or random (≥ 200 mg/dL) plasma glucose level; (2) on separate occasions, at least two elevated plasma glucose levels (fasting ≥ 140 mg/dL or random ≥ 200 mg/dL, or 200 mg/dL after 2 hours or more on glucose tolerance testing) in the absence of symptoms; or (3) treatment with a hypoglycemic medication. We excluded 63 cases of insulin-dependent diabetes and 7 women with gestational diabetes only. Further details of the classification of diabetes can be found elsewhere.^{11,12}

The validity of diabetes confirmation was documented with a random sample of participants reporting diabetes mellitus. Out of a sample of 84 women with con-

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TABLE 1—Distribution of Characteristics among 114 245 US Women,^a According to 1976 Smoking Status

			Current Smokers		
	Never Smokers	Ex-smokers	1-14 Cig/Day	15-24 Cig/Day	25 or More Cig/Day
Number	49 969	26 602	10 681	16 533	10 460
Mean age, y (SD)	42.2 (7.4)	42.4 (7.1)	41.8 (7.2)	42.3 (7.2)	42.7 (6.9)
Body mass index, kg/m ² (SD)	24.0 (4.2)	23.9 (4.1)	23.2 (3.9)	22.9 (3.5)	23.4 (4.0)
Family history ^b of diabetes, %	16.9	16.8	14.7	14.6	15.0
Alcohol use, ^c g/day (SD)	3.4 (7.7)	6.4 (10.5)	6.1 (10.7)	6.5 (11.8)	9.0 (15.5)
Physical activity, ^d times/week, %					
0	61.5	61.2	64.0	69.2	74.5
1-3	24.0	25.6	24.9	21.2	17.5
4+	14.5	13.2	11.1	9.6	8.0
Physician visits, ^e %					
0	42.8	41.1	44.2	45.1	43.5
1	20.9	21.0	21.4	21.5	20.5
2+	36.3	37.9	34.4	33.4	36.0

^aSample was of registered nurses, 30 to 55 years of age and free from cardiovascular disease, cancer, and diabetes at baseline.
^bA family history of diabetes is defined as a mother, father, sister, or brother with diagnosed diabetes (from the 1982 questionnaire).
^cAlcohol use was obtained from the 1980 questionnaire.
^dAverage number of weekly episodes of physical activity in which exercise lasted long enough to work up a sweat (from the 1980 follow-up questionnaire).
^eNumber of physician visits during the previous year (from the 1980 follow-up questionnaire).

firmed diabetes by supplementary questionnaire, 71 provided permission to obtain medical records and 62 of those (87%) had medical records available. Upon review of these records, an endocrinologist (J. E. M.), blinded to information on the supplementary questionnaire, was able to confirm a diagnosis of diabetes in 61 of the 62 women (98.4%).

Person-months of follow-up were accumulated for each risk factor, and risk factor status was updated every 2 years. For example, if a woman was smoking one pack of cigarettes per day in 1976, stopped in 1978, and was subsequently diagnosed with diabetes in 1984, she would contribute 2 years of person-time (1976 to 1978) to the 15 to 24 cigarettes-per-day category and 6 years of person-time (1978-1984) to the past smoking category. Because she was diagnosed with diabetes while being a past smoker, her diagnosis is counted in the incidence rate for past smokers, not current smokers. Women accumulated person-time of exposure until the date of diabetes, cancer, heart disease diagnosis, or death. Relative risks were calculated as the rate of disease among the exposed (total number of cases among smokers or past smokers divided

by the total person-time of exposure) divided by the rate of disease among the nonexposed (total number of cases among nonsmokers divided by the total nonsmoking person-time). We calculated these risks by using the Mantel-Haenszel summary statistic to adjust for deciles of body mass index (kilograms/square meters) and 5-year age intervals. We also calculated 95% confidence intervals and, where applicable, Mantel extension tests^{13,14} for trend across increasing dosage levels among current smokers. Cox proportional hazard models were used to control simultaneously for potential confounders.¹⁵

Results

Average age did not differ materially among women who were never smokers, past smokers, or current smokers. However, smokers did have a lower body mass index, lower frequency of a family history of diabetes, higher alcohol consumption, and reduced physical activity (Table 1). The distribution of characteristics were similar among the nondiabetic population.

During 1 277 589 person-years of follow-up, we confirmed 2333 incident cases

of noninsulin-dependent diabetes mellitus. The age- and relative weight-adjusted relative risk of this disease among women smoking 25 or more cigarettes, compared with never smokers, was 1.37 (95% CI = 1.16, 1.62) (Table 2). The test for trend was also significant among smokers (P trend = .005), indicating a dose-response association between number of cigarettes smoked and risk of the disease.

We previously found moderate inverse associations between physical activity,¹¹ specific nutrient intakes,¹⁶ alcohol consumption,¹⁷ and the risk of subsequent diabetes. Because information on diet, alcohol intake, and physical activity was first collected on the 1980 follow-up questionnaire, only incident cases after the return date of the 1980 questionnaire ($n = 1578$) were included in the multivariate models controlling for these and other risk factors (see Table 2). The multivariate relative risk of noninsulin-dependent diabetes mellitus among women smoking 25 or more cigarettes per day was 1.42 (95% CI = 1.18, 1.72) compared with never smokers. The relative risk of the disease was intermediate among past smokers (RR = 1.10; 95% CI = 1.00, 1.20). Relative risk estimates for smokers versus nonsmokers were not appreciably altered when total energy, energy-adjusted vegetable fat, potassium, calcium, magnesium, or self-reported hypertension were added to the statistical model. In addition, the 40% increase in risk of the disease among women smoking 25 or more cigarettes per day compared with never smokers was not affected when newly diagnosed cases of noninsulin-dependent diabetes mellitus who also had incident coronary heart disease, cancer, or stroke diagnosed in the same 2-year time interval were excluded.

Bias may occur if smokers experience an increase in other adverse health effects that heighten physician surveillance for diabetes and other medical conditions. Smokers did not have a larger number of physician visits (Table 1), even after the number of visits among the diabetes-free population during the 12-year follow-up period was tabulated. To reduce the potential for bias further, we calculated relative risk estimates of noninsulin-dependent diabetes mellitus among smokers, using only incident symptomatic cases of diabetes ($n = 1655$) and adjusting for age and body mass index. The relative risk of the disease was 1.41 (95% CI = 1.15, 1.72) among women smoking 25 or more cigarettes per day compared with never smokers (Table 2). Furthermore, after taking alcohol consumption into account (data

TABLE 2—Cigarette Smoking and Risk of Noninsulin-Dependent Diabetes among 114 247 US Women,^a during 12 Years of Follow-up

	Nonsmokers	Ex-smokers	Current Smokers			P Trend ^b
			1–14 Cig/Day	15–24 Cig/Day	25 or More Cig/Day	
Cases ^c	1 021	713	138	225	201	
Person-years	558 957	350 798	106 404	156 028	105 402	
All cases						
Age-adjusted relative risk (95% CI)	1.0 (Reference)	1.07 (0.98, 1.18)	0.73 (0.61, 0.88)	0.82 (0.71, 0.94)	1.08 (0.92, 1.25)	.001
Age- and body mass index-adjusted relative risk (95% CI)	1.0 (Reference)	1.13 (1.02, 1.25)	0.99 (0.81, 1.20)	1.28 (1.09, 1.50)	1.37 (1.16, 1.62)	.005
Multivariate relative risk ^d (95% CI)	1.0 (Reference)	1.10 (1.00, 1.20)	0.95 (0.76, 1.20)	1.19 (0.99, 1.43)	1.42 (1.18, 1.72)	.001
Symptomatic cases only ^e	711	519	87	159	148	
Age- and body mass index-adjusted relative risk (95% CI)	1.0 (Reference)	1.20 (1.06, 1.35)	0.92 (0.72, 1.18)	1.37 (1.14, 1.66)	1.41 (1.15, 1.72)	.005
Multivariate relative risk ^d (95% CI)	1.0 (Reference)	1.17 (1.02, 1.35)	0.90 (0.68, 1.19)	1.20 (0.96, 1.50)	1.49 (1.19, 1.87)	.005

^aSample was of registered nurses, 30 to 55 years of age and free from cardiovascular disease, cancer, and diabetes at baseline.

^bThe test for trend is calculated across increasing categories of smoking for current smokers only.

^cThirty-five cases had missing smoking information in 1976 and were excluded from person-month analysis for the first follow-up period.

^dThis includes only incident cases diagnosed after the return of the 1980 follow-up questionnaire (n = 1578 cases and n = 1112 for symptomatic cases only). Multivariate analysis controlling for age (5-year age groups), body mass index (deciles), family history of diabetes, menopause, postmenopausal hormone use (never, past, current), oral contraceptive use (never, past, current), alcohol (0, 0.1–4.9, 5.0–14.9, 15.0–24.9, 25+ g/day), and physical activity (0, 1, 2, 3, 4+ physical activity episodes/wk).

^eThirty-one cases had missing smoking information in 1976 and were excluded from person-month analysis for the first follow-up period.

available only after June 1, 1980), the multivariate relative risk was not appreciably different for the smaller subset of symptomatic cases (n = 1112) diagnosed after June 1, 1980 (RR = 1.49; 95% CI = 1.19, 1.87) (Table 2).

Obesity only slightly modified the association between smoking and diabetes. Among women with a body mass index not greater than 29.0 kg/m², the age- and obesity-adjusted relative risk of noninsulin-dependent diabetes mellitus was 1.23 (95% CI = 0.87, 1.74) for women smoking 25 or more cigarettes per day compared with never smokers (data not shown). Among women with a body mass index greater than 29.0 kg/m², the age- and obesity-adjusted relative risk of the disease was 1.40 (95% CI = 1.11, 1.75) for the same smoking level compared with never smokers.

Discussion

In these prospectively collected data, we observed a positive association between smoking and the risk of diabetes. The risk was more pronounced after we controlled for established predictors of the disease; it increased linearly with the num-

ber of cigarettes smoked and was only slightly modified by obesity.

Because overall follow-up of this cohort involved more than 90% of original respondents, the results are unlikely to be biased by losses to follow-up. As many as 50% of diabetes cases are undiagnosed¹⁸; consequently, biased surveillance among smokers could theoretically inflate the diagnosis rate in these groups. However, because smoking is not related to the number of physician visits (Table 1), biased surveillance is unlikely to explain the elevated risk of diabetes among smokers. Furthermore, restricting the outcome to symptomatic cases of diabetes does not appreciably alter the magnitude of the association. Previously, we reported a strong association between relative weight and incident diabetes.¹⁹ Even after controlling for deciles of relative weight, residual confounding may exist among the top deciles where the increased relative risk of diabetes is more than 20 times that for women in the lowest decile.¹⁹ However, because smoking is inversely related to body mass index,^{20,21} residual confounding by relative weight, if anything, attenuates the association between smoking and diabetes. Therefore, our results

may reflect an underestimate of the association between smoking and noninsulin-dependent diabetes mellitus.

In one other study, an association between smoking and diabetes was observed among men in the Zutphen study⁷; however, no association was seen in two others.^{8,9} Feskens and Kromhout⁷ followed 841 middle-aged men for 25 years and documented 58 new cases of diabetes. After they controlled for age, subscapular skinfold, resting heart rate, alcohol, and energy intake, the relative risk of developing diabetes was 3.3 (95% CI = 1.4, 7.9) among men smoking 20 cigarettes per day compared with nonsmokers. Wilson et al.⁹ followed 1320 women for 8 years in the Framingham Heart Study and found that, among the 38 new cases of diabetes, the baseline rate of smoking did not differ from that in the reference population of nondiabetics after controlling for age, body mass index, lipoprotein profile, blood pressure, and diuretic use. Similarly, in a 5-year follow-up of 8688 men in the Israeli Ischemic Heart Disease Project, Medalie et al.⁸ reported no increased risk of diabetes among current smokers as compared with nonsmokers after controlling for age, body mass index, peripheral

vascular disease, cholesterol, blood pressure, uric acid, hemoglobin, country of birth, and educational status. Previous studies have been small and have controlled for only three or four obesity categories and not for family history of diabetes, physical activity, and alcohol intake (except for the Zutphen study).⁷ Therefore, the association between smoking and diabetes in these studies may have been missed.

Although smoking is generally inversely associated with body mass index, Shimokata et al.³ reported an increase in the waist-to-hip ratio among men who started smoking; this increase was noted despite the subjects' weight loss. Among women, smoking may have an "anti-estrogenic" effect, causing adverse changes in the waist-to-hip ratio.^{3,22,23} An increased waist-to-hip ratio, a marker of the ratio of intra-abdominal to subcutaneous fat, has been shown to be significantly positively correlated with insulin resistance,²⁴ plasma glucose levels (after oral glucose load),²⁵ and overt diabetes.^{5,6} Therefore, the effect of smoking on the development of diabetes may be mediated through alterations in fat distribution. Smoking may also be directly toxic to pancreatic tissue. The risk of pancreatic cancer is elevated among smokers^{26,27} and the diabetic population.^{27,28} Thus, biological mechanisms that explain the association between smoking and diabetes may also play a role in development of pancreatic cancer. Further investigation of the interrelationships between smoking, relative weight, and fat distribution and the subsequent development of diabetes is needed to help clarify these mechanisms.

In conclusion, after controlling for known predictors of diabetes, we found a moderate association between smoking and the subsequent risk of diabetes. Our findings from this large prospective cohort of women provide new evidence that cigarette smoking may be a modifiable risk factor that could be targeted for diabetes prevention. □

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