Smoking and Risk of Coronary Heart Disease Among Women With Type 2 Diabetes Mellitus

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Background: Although the association between smoking and increased risk of coronary heart disease (CHD) is well established in the general population, this relationship is less well-defined among individuals with diabetes.

Objective: To assess the relationship between cigarette smoking and risk of CHD among women with type 2 diabetes mellitus in the Nurses’ Health Study cohort.

Methods: The Nurses’ Health Study, a prospective cohort study of 121700 US female registered nurses surveyed in 11 states and followed up from July 1, 1976, through July 1, 1996, involved a total of 6547 women diagnosed as having type 2 diabetes mellitus. Incident cases of CHD were our main outcome measure in this study.

Results: We documented 458 incident cases of CHD (200 fatal CHD-related cases and 258 nonfatal myocardial infarctions) during 20 years (68227 person-years) of follow-up. We found a dose-response relationship between current smoking status and risk of CHD among diabetic women. Compared with never smokers, the relative risks (RRs) for CHD were 1.21 (95% confidence interval [CI], 0.97-1.51) for past smokers, 1.66 (95% CI, 1.10-2.52) for current smokers of 1 to 14 cigarettes per day, and 2.68 (95% CI, 2.07-3.48) for current smokers of 15 or more cigarettes per day in multivariate analyses (P<.001 for trend). The multivariate RR of CHD among diabetic women who had stopped smoking for more than 10 years was similar to that among diabetic women who were never smokers (RR, 1.01; 95% CI, 0.73-1.38). In secondary analyses involving diabetic and nondiabetic women, the multivariate-adjusted RR of CHD for those with diabetes who currently smoked (≥15 cigarettes per day) compared with those who never smoked was 7.67 (95% CI, 5.88-10.01).

Conclusions: Cigarette smoking is strongly associated with an increased risk of CHD among women with type 2 diabetes mellitus. Furthermore, quitting smoking seems to decrease this excess risk substantially; women with diabetes should be strongly advised against smoking.

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SUBJECTS AND METHODS

STUDY POPULATION

The Nurses’ Health Study was established in 1976, when 121,700 US female registered nurses aged 30 to 55 years who each resided in 1 of 11 states completed a mailed questionnaire regarding medical history and lifestyle factors. This information has been updated every 2 years. The population for this analysis included women who were diagnosed as having type 2 diabetes mellitus at baseline or during follow-up between July 1, 1976, and July 1, 1996.

ASSESSMENT OF SMOKING

Smoking status was assessed on each biennial questionnaire. Participants were classified as current, past, or never smokers. Current smokers were categorized into those who smoked 1 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, or 45 or more cigarettes per day. In this study, these categories were collapsed into 1 to 14 and 15 or more cigarettes per day because of the small number of cases. For time since quitting, former smokers were categorized as having stopped smoking for 1 to 3, 5 to 6 to 10, 11 to 15, and more than 15 years. The last 2 categories were also combined to assess the effect of quitting for more than 10 years. Coronary heart disease–related events were allocated to the smoking exposure status defined on the most recent questionnaire.

DOCUMENTATION OF DIABETES

When a participant reported a diagnosis of diabetes, we mailed her a supplementary questionnaire requesting information on the details of the diagnosis (ie, diagnostic tests, symptoms, and year of diagnosis) and therapy (insulin or oral hypoglycemic treatment). Using the National Diabetes Data Group criteria,8 diabetes was considered confirmed if the questionnaire indicated one of the following: (1) classic symptoms (excessive thirst, polyuria, weight loss, and hunger) associated with an elevated plasma glucose level (fasting value, ≥141 mg/dL [≥7.8 mmol/L]; random value, ≥200 mg/dL [≥11.1 mmol/L]; or a ≥2-hour postglucose challenge value of ≥200 mg/dL [≥11.1 mmol/L]); (2) there were no symptoms, but at least 2 plasma glucose values were elevated by the criteria previously described on different occasions; or (3) treatment with a hypoglycemic medication (insulin or an oral hypoglycemic agent).

We depended on self-reported information for the diagnosis of diabetes by these nurses, but validated the reports in a random sample of women by obtaining their medical records. Among 84 women classified by the supplementary questionnaire as having type 2 diabetes mellitus, 71 provided permission to review their medical records and 62 had records available. An endocrinologist (J.E.M.) blinded to the information reported on the supplementary questionnaire reviewed the records according to the National Diabetes Data Group criteria. The diagnosis of type 2 diabetes mellitus was confirmed in 61 (98%) of the 62 women.

Those with diabetes diagnosed before the age of 30 years (most likely type 1 diabetes mellitus) or a previous diagnosis of cancer or cardiovascular disease (CVD) were excluded from all analyses. In the primary analyses, self-reported diabetes was used to define the analytic cohort (n=6547 diabetic women). Secondary analyses including only diabetic cases confirmed by the supplementary questionnaire (n=4863) yielded similar results.

DIAGNOSIS OF CHD

The primary end point in our analysis was incident CHD (including nonfatal myocardial infarction [MI] and fatal CHD). We analyzed stroke and total CVD (CHD and stroke) as secondary end points. All CVD-related cases were included in the analysis if they were diagnosed after the 1976 questionnaire, and after the diagnosis of diabetes. Women who reported a nonfatal MI were asked permission to review their medical records, which were used to confirm the diagnosis according to the World Health Organization diagnostic criteria (ie, symptoms plus either cardiac enzyme level elevations or diagnostic electrocardiographic changes). Physicians blinded to exposure status conducted the record reviews. Infarctions were classified as probable if a patient required hospital admission, and confirmatory information was obtained by interview or letter without medical records. All confirmed and probable nonfatal MI cases included in the analyses.

fatal MI was somewhat stronger than for fatal CHD (Table 2). Further adjustment for vitamin E supplement use did not alter the results. Current smokers had an RR of 2.17 of developing CHD compared with nonsmokers (never smokers). Women who had stopped smoking within the past 10 years still had an increased risk (RR, 1.32 [95% CI, 0.96-1.84] for those who quit for 6-10 years; and RR, 1.40 [95% CI, 1.04-1.88] for those who quit for 1-5 years) compared with the never smokers. Nevertheless, the latter 2 groups of past smokers were still at a lower risk compared with current smokers.

In secondary analyses, we examined smoking in relation to the risk of stroke and total CVD (stroke and CHD). The multivariate RRs for stroke were 0.69 (95% CI, 0.48-1.00) among past smokers, 1.04 (95% CI, 0.50-2.17) among current smokers of 1 to 14 cigarettes per day, and 1.84 (95% CI, 1.21-2.81) among current smokers of 15 or more cigarettes per day (P=.004 for trend). The multivariate RRs of CVD were 1.03 (95% CI, 0.86-
Statistical Analysis

Participants contributed person-time from the date of return of the 1976 questionnaire (for those with prevalent diabetes) or from the date of diabetes diagnosis (for those with incident diabetes) until the date of occurrence of MI, the date of death from CHD, or June 1, 1996, whichever came first. Incident cases of CHD were allocated to the exposure status defined in the most recent questionnaire. For comparison of the excess risk of smoking among diabetic and nondiabetic women, incidence rates of CHD were calculated by dividing the number of new cases by the accumulated person-time of follow-up and were adjusted to the age distribution of diabetic and nondiabetic women by direct standardization.

Relative risks were calculated as the incidence rate in each smoking category divided by the corresponding rate among never smokers. All relative risks (RRs) were age adjusted, and 95% confidence intervals (CIs) were calculated.

1.25) for past smokers, 1.46 (95% CI, 1.02-2.10) for current smokers of 1 to 14 cigarettes per day, and 2.42 (95% CI, 1.94-3.02) for current smokers of 15 or more cigarettes per day (P < .001 for trend).

We also compared age-adjusted rates of CHD in women with diabetes with those in nondiabetic women according to smoking status. The age-adjusted incidence rate of CHD among diabetic women was much higher than that of nondiabetic women of similar smoking status (Figure 2). The joint impact of smoking and diabetes status on the risk of CHD was substantial; compared with nondiabetic women who had never smoked, diabetic women who smoked 15 or more cigarettes per day had an age-adjusted RR of 19.01 (95% CI, 15.42-23.45). This RR was attenuated to 7.67 (95% CI, 5.88-10.01) in the multivariate-adjusted model. Among nondiabetic women, the multivariate RR comparing current smokers (≥15 cigarettes per day) with never smokers was 5.13 (95% CI, 4.53-5.80). The corresponding RR among diabetic women was 2.65 (95% CI, 2.06-3.40). The likelihood ratio test and interaction was significant (P < .001). The higher RR of CHD of nondiabetic women who smoked compared with diabetic women who smoked can be explained by the much higher baseline risk of diabetic women compared with nondiabetic women.

We observed a strong positive association between cigarette smoking and CHD among diabetic women. Cigarette smoking amplified the excess risk of CHD associated with type 2 diabetes mellitus. On the other hand, smokers who quit smoking for more than 10 years had a...
The strengths of the study include the large number of diabetic women and the long duration of follow-up, which allows the assessment of smoking and CHD risk in different subgroups. The follow-up rate for fatal and nonfatal events was high (approximately 98%), minimizing potential bias due to loss to and unavailability for follow-up. The prospective design minimized selection and recall bias, which can occur in case-control studies. Potential weaknesses should be noted. Some women with diabetes may have been undiagnosed in the cohort because we did not screen for glucose intolerance. However, these cases would not alter the case status of women reporting a diagnosis of diabetes, which was validated in a separate study.9 The criteria for type 2 diabetes mellii-
tus have recently changed, so that those with a glucose level higher than 126 mg/dL (7.0 mmol/L) are believed to have diabetes, instead of the 141 mg/dL (7.8 mmol/L) used before the publication of the new criteria in 1997. So, more nondiabetic persons would be classified as having diabetes using the new definition. Nevertheless, inclusion of diabetic persons in the nondiabetic group in our study as a result of using the old definition would have attenuated the associations we observed and is unlikely to change our findings.

The smoking assessment was based on self-reports and was not verified by other objective measures. However, reporting of smoking should not be biased in relation to CHD incidence because smoking was assessed before the development of CHD. In addition, because the smoking variable was updated every 2 years, our analyses were able to take into account changes in smoking behavior.

Few previous studies have prospectively examined the association between smoking and CHD among diabetic persons. A Finnish prospective study among 313 men and women with type 2 diabetes mellitus did not find smoking to be related to fatal or nonfatal CHD in a univariate logistic regression analysis. Also, in the Whitehall study, smoking was not significantly associated with CHD-related mortality rates among 224 diabetic and glucose-intolerant men. Both studies involved fewer diabetic subjects and had a shorter follow-up than our study; thus, statistical power to detect an association was limited. On the other hand, in the National Health and Nutrition Examination Survey study, CHD-related mortality risk was higher among 492 diabetic smokers compared with never smokers, and in the Multiple Risk Factor Intervention Trial, risk of CVD-related mortality among 5625 diabetic men increased with higher levels of smoking. This was also supported more recently by the results from the United Kingdom Prospective Diabetes Study, in which smoking was a significant risk factor for fatal and nonfatal MI (P = .02) among diabetic women and men in multivariate analyses.

Diabetes may increase the risk of CHD through various proposed mechanisms, including lipoprotein changes, increased vascular endothelial injury and permeability, thrombotic disorders, increased oxidative stress, and fibrinolytic factors and platelet activities leading to atheroma formation. Smoking may exacerbate these conditions and contribute to a dramatically increased risk

<table>
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<tr>
<th>Variable</th>
<th>Never Smokers</th>
<th>Past Smokers</th>
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<th>≥15</th>
<th>P Value for Interaction</th>
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<td>&lt;25</td>
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<td>1.51 (0.66-3.45)</td>
<td>1.99 (1.15-3.45)</td>
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<td>1.34 (0.82-2.18)</td>
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<td>≤10</td>
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<td>1.24 (0.87-1.76)</td>
<td>1.24 (0.65-2.36)</td>
<td>3.29 (2.34-4.65)</td>
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<tr>
<td>≥60</td>
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<td>1.18 (0.88-1.57)</td>
<td>2.15 (1.24-3.72)</td>
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<td>1.64 (0.68-3.98)</td>
<td>3.65 (2.15-6.19)</td>
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<td>1.13 (0.76-1.68)</td>
<td>1.29 (0.58-2.88)</td>
<td>3.03 (1.94-4.73)</td>
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<td>1.80 (0.87-3.73)</td>
<td>1.68 (0.57-4.96)</td>
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</table>

*The covariates for the multivariate adjustment are the same as those given in the first footnote to Table 2, excluding the stratifying variable. RR indicates relative risk, CI, confidence interval; CHD, coronary heart disease; BMI, body mass index; and MI, myocardial infarction.
†Reference group.
‡Included treatment with insulin or oral hypoglycemic medications.
The benefits of smoking cessation are associated with total risk of developing CHD among diabetic women who smoked. More than 10 years seem to substantially reduce the high risk among women. \( \text{RR, 1.94; 95\% CI, 1.25-3.03} \). 

In previous studies, smoking rates among diabetic persons were higher among diabetic persons than those in the nondiabetic population. It is alarming that others found smoking rates among diabetic persons to be similar to or even higher than those of nondiabetic persons. However, individuals with diabetes seem to be more receptive to their physician’s advice and to the prospect of smoking cessation.

Smoking cessation may have an important effect on CHD risk reduction among diabetic persons compared with the effects reported with cholesterol lowering or high blood pressure treatment. Clinical trials to lower cholesterol levels among diabetic persons achieved 25% to 55% reduction in the risk of major CHD-related events, and tight blood pressure control achieved 21% reduction in the risk of fatal and nonfatal MI and sudden death (although the results were not statistically significant).

Our results suggest that the risk of CHD among diabetic women who smoke could have been reduced by about 54% if they had not smoked. In the overall diabetic population, which comprises 20% smokers, the population attributable risk due to current smoking was 19%.

Our findings have important clinical and public health implications and provide strong support for the American Diabetic Association recommendations. Given that cigarette smoking is such a strong, yet modifiable, risk factor for CHD among diabetic individuals, physicians should discourage their diabetic patients from smoking.

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