Smoking and Mortality Among Women With Type 2 Diabetes

The Nurses’ Health Study cohort

OBJECTIVE — To assess the relationship between cigarette smoking and mortality among women with type 2 diabetes in the Nurses’ Health Study cohort.

RESEARCH DESIGN AND METHODS — The Nurses’ Health Study, a prospective cohort of U.S. female registered nurses, included 7,401 women with type 2 diabetes diagnosed at baseline or during follow-up from 1976 to 1996. Total and cause-specific mortality of these diabetic women were the outcomes of interest.

RESULTS — We documented 724 deaths during 20 years of follow-up (67,420 person-years) among women with type 2 diabetes. In multivariate analyses, adjusting for age, history of high blood pressure and high cholesterol, and other cardiovascular risk factors, compared with never smokers, the RRs of mortality were 1.31 (95% CI 1.11–1.55) for past smokers, 1.43 (0.96–2.14) for current smokers of 1–14 cigarettes/day, 1.64 (1.24–2.17) for current smokers of 15–34 cigarettes/day, and 2.19 (1.32–3.65) for current smokers of ≥35 cigarettes/day (P for trend = 0.0002). Women with type 2 diabetes who had stopped smoking for ≥10 years had a mortality RR of 1.11 (0.92–1.35) compared with diabetic women who were never smokers.

CONCLUSIONS — Cigarette smoking is associated in a dose-response manner with an increased mortality among women with type 2 diabetes. Furthermore, quitting smoking appears to decrease this excess risk substantially. Diabetes patients should be strongly advised against smoking.

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Although cigarette smoking is a major risk factor for total mortality in the general population (1), and patients with diabetes are at higher mortality risks than those without diabetes (2,3), prospective data on smoking and mortality among individuals with type 2 diabetes are sparse. Whereas some studies failed to find an association (4,5), others found a significant association between smoking and mortality among diabetic patients (6–10). The only study to follow a large number of diabetes patients (5,163 diabetic men) and include quantitative smoking data to assess the risk of cardiovascular mortality failed to account for change in smoking habits, because it used baseline smoking data (11).
since quitting, former smokers were categorized as having stopped smoking for 1–4, 5–9, or ≥10 years. Mortality outcome was allocated to the smoking exposure status defined on the most recent questionnaire.

During follow-up, for any participant who was a never smoker or who quit smoking for >10 years and failed to provide an update on current smoking status at any cycle, the previous smoking status (never or past smoker) was carried forward, because it was unlikely that such a person would initiate smoking at this late age. For current smokers or those who quit for <10 years and failed to provide an update on their smoking status at any cycle, the previous smoking status was carried forward only one cycle and then considered as missing for subsequent missing cycles. Therefore, 166 cases subjects (7,730 person-years) with missing and insufficient information on smoking status were excluded.

Documentation of diabetes
When a participant reported a diagnosis of diabetes, we mailed a supplementary questionnaire requesting information on the details of the diagnosis (i.e., diagnostic tests, symptoms, and year of diagnosis) and therapy (insulin or oral hypoglycemic treatment). Diabetes was considered confirmed if the questionnaire indicated one of the following National Diabetes Data Group (NDDG) criteria (15): 1) classic symptoms (excessive thirst, polyuria, weight loss, and hunger) associated with an elevated plasma glucose level (fasting value ≥7.8 mmol/l, random value ≥11.1 mmol/l, or a ≥2-h postglucose challenge value of ≥11.1 mmol/l); 2) no symptoms, but at least two plasma glucose values elevated by the above criteria on different occasions; or 3) treatment with hypoglycemic medication (insulin or 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, 71 provided permission to review their medical records, and 62 had records available. An endocrinologist (J.E.M.) who was blinded to the information reported on the supplementary questionnaire reviewed the records according to NDDG criteria. The diagnosis of type 2 diabetes was confirmed in 61 (98%) of the 62 women (16).

Those with diabetes diagnosed before the age of 30 years (most likely to have type 1 diabetes) or a diagnosis of cancer or cardiovascular disease before 1976 were excluded from all analyses. In the primary analyses, self-reported diabetes was used to define the analytic cohort (n = 7,401 women with diabetes). Secondary analyses, including only subjects with diabetes confirmed by the supplementary questionnaire (n = 5,541), yielded similar results.

Mortality outcome
The primary end point in our analysis was death from all causes occurring after the 1976 questionnaire was returned but before 1 June 1996. The deaths were further grouped into total cardiovascular diseases (ICD-8 410–440 and 793), total cancers (ICD-8 140–207), and total deaths excluding lung cancer (excluding ICD-8 140–161 and 163–202). The latter category was used to determine whether total cancer mortality was strongly influenced by the relation between lung cancer and smoking.

The mortality surveillance included systematic searches of the vital records of the states using the National Death Index to discover deaths among women who did not respond during each questionnaire cycle. This search was supplemented by reports from relatives and postal authorities. Physicians reviewed death certificates to classify individual causes of death. We estimate that >98% of the deaths in the cohort were ascertained by these methods (17).

Statistical analysis
Participants contributed person-time from the date of return of the 1976 questionnaire (for prevalent diabetes) or from the date of diabetes diagnosis (for incident diabetes) until the date of death or 1 June 1996, whichever came first. Mortality rates were calculated by dividing the number of new deaths by the cumulative person-time of follow-up and were adjusted to the age distribution by direct standardization.

RRs were calculated as the mortality rate in each smoking category divided by the corresponding rate among never smokers. All RRs were age-adjusted, and 95% CIs were calculated. Population attributable risk was calculated by using the formula provided by Rothman and Greenland (18) to determine the fraction of premature deaths in the study population that would not have occurred if exposure had not existed.

Pooled logistic regression models with 2-year time increments were used to simultaneously control for known mortality risk factors. At the beginning of each 2-year time period, person-time was allocated to status of the covariates. Most of the covariates were updated biennially, including age, postmenopausal hormone use, alcohol use, duration of diabetes, BMI, physical activity, diabetes medication, parental history of myocardial infarction (MI) before the age of 60, and history of physician-diagnosed high cholesterol and high blood pressure. The self-reports of the latter two conditions were shown to be highly valid in an earlier study (19). Two covariates were also used for stratified analyses to assess potential effect modification: parental history of MI (yes, no) and the duration of diabetes (≤10 years; >10 years).

The likelihood ratio test was used to check for interactions between diabetes status and smoking (18). The test was conducted by taking the difference in the −2 log likelihood score between the model containing the interaction terms and the one excluding them and comparing that value to a χ² distribution with 4 degrees of freedom. Tests for trend were conducted to assess the dose-response relation across smoking categories. All P values were two-sided.

RESULTS — At baseline, 1,752 women reported physician-diagnosed diabetes at age ≥30 years. During follow-up, an additional 5,649 women reported a diagnosis of diabetes. During the follow-up among these women, which lasted up to 20 years (from 1976 to 1996; 67,420 person-years), we documented 724 deaths.

The characteristics of the women with diabetes in relation to their smoking habits in 1986 (which is the midpoint of the follow-up period) are shown in Table 1. They indicate that most variables were similarly distributed among the different smoking status categories, although current smokers were more likely to consume alcohol, and heavy smokers were more likely to be treated with oral hypoglycemic drugs and less likely to be treated with insulin (Table 1). Compared
Table 1—Age-adjusted characteristics of diabetic women according to smoking status in 1986

<table>
<thead>
<tr>
<th></th>
<th>Never smokers</th>
<th>Past smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,593</td>
<td>1,240</td>
<td>196</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>62.6 (95% CI)</td>
<td>62.5 (95% CI)</td>
<td>62.6 (95% CI)</td>
</tr>
<tr>
<td>BMI (m/kg²)</td>
<td>29.3 (95% CI)</td>
<td>29.8 (95% CI)</td>
<td>27.1 (95% CI)</td>
</tr>
<tr>
<td>Mean duration of diabetes (year)</td>
<td>9.2 (95% CI)</td>
<td>8.8 (95% CI)</td>
<td>9.7 (95% CI)</td>
</tr>
<tr>
<td>Mean alcohol consumption (g)</td>
<td>2.0 (95% CI)</td>
<td>3.3 (95% CI)</td>
<td>5.5 (95% CI)</td>
</tr>
<tr>
<td>History of high blood pressure (%)</td>
<td>55 (95% CI)</td>
<td>60 (95% CI)</td>
<td>46 (95% CI)</td>
</tr>
<tr>
<td>History of high cholesterol (%)</td>
<td>25 (95% CI)</td>
<td>30 (95% CI)</td>
<td>27 (95% CI)</td>
</tr>
<tr>
<td>Current postmenopausal hormone use (%)</td>
<td>16 (95% CI)</td>
<td>16 (95% CI)</td>
<td>12 (95% CI)</td>
</tr>
<tr>
<td>Insulin use (%)</td>
<td>18 (95% CI)</td>
<td>19 (95% CI)</td>
<td>14 (95% CI)</td>
</tr>
<tr>
<td>Parental history of MI (%)</td>
<td>23 (95% CI)</td>
<td>24 (95% CI)</td>
<td>18 (95% CI)</td>
</tr>
</tbody>
</table>

The 1986 questionnaire was used as the middle year to represent the overall follow-up period for characteristics of the study population. *Based on women who answered the 1986 smoking questionnaire; † insulin and oral hypoglycemic use was based on 1988 data. Cig, cigarette.

Table 2—Age- and multivariate-adjusted* RRs of total and cause-specific mortality according to smoking status among diabetic women (n = 7,401)

<table>
<thead>
<tr>
<th></th>
<th>Never smokers</th>
<th>Past smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>329</td>
<td>283</td>
<td>130</td>
</tr>
<tr>
<td>Case subjects</td>
<td>33,122</td>
<td>23,599</td>
<td>33,122</td>
</tr>
<tr>
<td>Person-years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.19 (95% CI)</td>
<td>1.14 (95% CI)</td>
<td>1.14 (95% CI)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.13 (95% CI)</td>
<td>1.43 (95% CI)</td>
<td>1.64 (95% CI)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>130</td>
<td>111</td>
<td>10</td>
</tr>
<tr>
<td>Case subjects</td>
<td>33,122</td>
<td>23,599</td>
<td>33,122</td>
</tr>
<tr>
<td>Person-years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.18 (95% CI)</td>
<td>1.08 (95% CI)</td>
<td>1.58 (95% CI)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.30 (95% CI)</td>
<td>1.58 (95% CI)</td>
<td>2.56 (95% CI)</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>106</td>
<td>96</td>
<td>8</td>
</tr>
<tr>
<td>Case subjects</td>
<td>33,122</td>
<td>23,599</td>
<td>33,122</td>
</tr>
<tr>
<td>Person-years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.24 (95% CI)</td>
<td>1.03 (95% CI)</td>
<td>1.09 (95% CI)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.31 (95% CI)</td>
<td>1.09 (95% CI)</td>
<td>1.13 (95% CI)</td>
</tr>
<tr>
<td>Cancer mortality (excluding lung cancer)</td>
<td>103</td>
<td>83</td>
<td>11</td>
</tr>
<tr>
<td>Case subjects</td>
<td>33,122</td>
<td>23,597</td>
<td>33,122</td>
</tr>
<tr>
<td>Person-years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age-adjusted RR</td>
<td>1.11 (95% CI)</td>
<td>0.79 (95% CI)</td>
<td>0.85 (95% CI)</td>
</tr>
<tr>
<td>Multivariate RR</td>
<td>1.17 (95% CI)</td>
<td>0.79 (95% CI)</td>
<td>0.76 (95% CI)</td>
</tr>
</tbody>
</table>

Data are RR (95% CI) unless otherwise indicated. *Covariates are time period (1976–1978, 1978–1980, 1980–1982, 1982–1984, 1984–1986, 1986–1988, 1988–1990, 1990–1992, 1992–1994, and 1994–1996); age (<50, 50–54, 55–59, 60–64, and 65+ years), postmenopausal hormone use (premenopausal status, never used, current use and past use), alcohol use (0, 1–4, 5–9, 10–14, and 15+ g/day), duration of diabetes (0, 5, 6–10, 11–15, and >15 years), and BMI (21, 22, 23–24, 25–28, and 29+ kg/m²). Physical activity (sedentary, light, moderate, and vigorous), diabetes medication (none, oral medication only, and insulin use), and parental history of MI before the age of 60 (yes, no), history of physician-diagnosed high cholesterol (yes, no), and history of physician-diagnosed high blood pressure (yes, no). † For trend analyses, the median value for each smoking category was used as a continuous variable (0 for never smokers, 1 for past smokers, and median number of cigarettes among smoking categories). Cig, cigarette.
1.64 (1.24–2.17) for current smokers of 15–34 cigarettes/day, and 2.19 (1.32–3.65) for current smokers of ≥35 cigarettes/day in multivariate analyses ($P$ for trend <0.0002) (Table 2). Both cardiovascular and cancer mortality were significantly associated with increasing smoking ($P$ values for trend were 0.0005 and 0.0001, respectively, in multivariate regression models), although the CIs included the null values in some smoking strata because of the small number of case subjects. For cancer mortality, the RR for women smoking ≥35 cigarettes was substantially elevated compared with the other categories, and the trend remained significant after exclusion of lung cancer cases, although the CIs were attenuated as a result of removing the influence of the strong smoking and lung cancer association. Women who had stopped smoking for ≥10 years had only a slight increase in risk (RR 1.11 [0.92–1.35]) compared with never smokers. However, significant elevations in risk remained in those who had quit more recently (Fig. 1).

The mortality risk attributable to current smoking in this population of women with diabetes was 16% (current smoking prevalence 23%). In analyses stratified by parental history of MI and duration of diabetes, consistent associations existed between smoking and total mortality risk.

We assessed the pack-years variable of smoking in relation to mortality risk among women with diabetes. Compared with never smokers, the multivariate-adjusted RRs across categories of pack-years were 0.92 (0.72–1.17) for 1–13 pack-years, 1.16 (0.82–1.64) for 14–24 pack-years, 1.69 (1.22–2.34) for 25–49 pack-years, and 1.95 (1.15–3.30) for ≥50 pack-years, $P$ for trend <0.0001.

We also compared age-adjusted rates of mortality in diabetic women with those in nondiabetic women according to smoking status. At each level of smoking, the age-adjusted mortality rate for women with diabetes was much higher than that for women without diabetes (Fig. 2); however, as observed in the figure, among nondiabetic subjects, the relative mortality risk among heavy smokers compared with never smokers was almost threefold, whereas it was only twofold for diabetic subjects. The test for interaction between diabetes status and smoking categories was not significant ($P$ = 0.83). The lower RR among diabetic subjects was probably due to the higher baseline risk of nonsmoking diabetic subjects. Absolute excess mortality risk of smoking among diabetic subjects was 765 deaths per 100,000 person-years (972/100,000 – 207/100,000 person-years) compared with an absolute excess mortality risk among nondiabetic subjects of 271 deaths per 100,000 person-years (379/100,000 – 108/100,000 person-years).
This shows a substantially higher excess mortality attributable to smoking among diabetic subjects compared with nondiabetic subjects.

CONCLUSIONS — A strong and consistent positive association between cigarette smoking and mortality rates among women with diabetes was observed in this study. Cigarette smoking increased the already elevated risk of mortality associated with type 2 diabetes, but quitting smoking for ≥10 years virtually eliminated the excess mortality associated with smoking.

Strengths of the study include the large number of diabetes case subjects and long duration of follow-up compared with other published studies, which allows for the assessment of smoking and mortality risk in different subgroups. Follow-up for mortality was high, minimizing potential bias cause by loss to 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 would not alter case status of women reporting a diagnosis of diabetes, which was validated in a separate substudy (16). Smoking assessment was based on self-reports and was not verified by other objective measures. However, because the smoking variable was updated every 2 years, our analyses were able to take into account changes in smoking behavior. Finally, our interaction test of smoking and diabetes was not significant on the RR scale, although the excess mortality attributable to smoking was much greater among diabetic subjects than nondiabetic subjects. This may be related to the inadequacy of the likelihood ratio test to detect this interaction (18).

Several cohort studies among people with diabetes have failed to find a significantly increased risk of coronary heart disease (CHD) mortality or total mortality rates among smokers (4,5,20,21). However, all of these studies had a small number of subjects, and some used a dichotomous smoking exposure (20), whereas others only adjusted for age in the model (21). Our findings were generally consistent with previous studies that found increased mortality risk in relation to smoking among diabetic patients (6–11). A 6-year mortality risk of 1.6 (1.13–2.22) was reported among diabetes patients who smoked compared with nonsmokers in one follow-up (7), whereas all-cause mortality among 602 diabetic patients was 1.8 times higher among smoking vs. nonsmoking patients in another study (8). Similar findings were reported for CHD mortality in the Multiple Risk Factor Intervention Trial (11), the Paris prospective study (9), the National Mortality Followback Survey (10), and in earlier analyses from the Nurses’ Health Study (6).

The duration of time since smoking cessation was linearly associated with decreased mortality risk in our study. This finding was supported by Yudkin (22) in the Multiple Risk Factor Intervention Trial, where he found a mean reduction of mortality of 20.8 per 1,000 among diabetic patients followed-up for 10 years, and he estimated that stopping smoking in a 45-year-old diabetic man would prolong his life by a mean of 3 years. In our results, smoking cessation after ≥10 years virtually abolished the excess mortality risk associated with smoking. Similar results were found in a cohort study of 4,427 diabetes patients by Chaturvedi et al. (23) in the World Health Organization Multinational Study of Vascular Disease in Diabetes cohort; quitting for ≥10 years was associated with a mortality risk of 1.25 (1.02–1.52). This slight elevation in risk could be related to the long-term effects of smoking on lung and other cancers.

Although the direct mechanisms by which smoking contributes to mortality among diabetic patients is not well understood, it is expected that smoking would accelerate diabetic angiopathy by impairing endothelial function (24–26). It has also been suggested that smoking affects the fibrinolytic system (24), which leads to high serum fibrinogen levels even after 5–10 years of cessation (27,28). Long-term effects of smoking (increased triglycerides, decreased HDL levels, and other metabolic effects that lead to atherogenesis) (29,30) on the cardiovascular system may not be reversible. Smoking has also been related to increased risk of diabetic nephropathy (13,14,31) and is thought to increase insulin resistance and exacerbate metabolic disturbances among diabetic patients (32–34). For cancer mortality, the mechanisms by which tobacco constituents induce or promote cancers among the general population (direct tissue contact, depressed immunological activity, genotoxicity, lowering circulating antioxidant levels, and other metabolic mechanisms) (35) are expected to be similar for diabetic patients.

In conclusion, mortality rates among women with diabetes are strongly related to their smoking habits, with heavier smokers having a twofold higher risk than never smokers. Excess risks were seen for cardiovascular and cancer mortality. Much higher excess mortality rates were observed among diabetic women who smoked compared with nondiabetic women. Furthermore, among diabetic patients, women who quit smoking had a substantially reduced mortality risk compared with those who continued smoking. The prevalence of smoking is still high among diabetic patients (11,33), although several studies have indicated that patients with diabetes are more motivated to quit smoking than healthy individuals (36,37). Therefore, greater efforts are needed to decrease smoking in this high-risk population.

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