Diabetes and the Risk of Lung Cancer

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OBJECTIVE — The incidence of some cancers has been reported to be higher in diabetic patients than in the general population. We estimated the incidence of lung cancer in diabetic patients and investigated the hypothesis that the rate of lung cancer is different in diabetic compared with nondiabetic patients.

RESEARCH DESIGN AND METHODS — Diabetic patients and age-, sex-, and general practice–matched nondiabetic control subjects were identified from U.K. computerized general practice records (General Practice Research Database), and these records searched for any incident lung cancer, demographic details, and smoking status. Primary lung cancer incidence was calculated and rates compared between diabetic patients and nondiabetic control subjects using multivariate Cox regression, adjusting for age, sex, and smoking. The comparison was repeated for incident diabetic patients followed from diagnosis and after stratifying by diabetic treatment.

RESULTS — The incidence of primary lung cancer in all 66,848 diabetic patients was 1.63 per 1,000 patient-years (95% CI 1.48–1.79) and 2.05 per 1,000 patient-years (1.76–2.38) among diabetic patients followed from diagnosis. When compared with nondiabetic control subjects, the hazard ratio was 0.88 (0.79–0.97) for all diabetic patients and 1.12 (0.95–1.34) for those followed from diagnosis. When observation was truncated to allow for shorter life expectancy, the hazard ratio for the total cohort was 0.98 (0.84–1.13), and no association was found with any treatment group.

CONCLUSIONS — No increased risk of lung cancer in diabetes was found. We hypothesize that the lower incidence may be partly due to shorter life expectancy.

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The incidence of lung cancer in subjects with diabetes might be different from that in the general population. Smoking is the major risk factor for lung cancer, and both insulin resistance (1) and type 2 diabetes (2,3) have been reported to be increased in smokers. Epidemiological studies have found positive associations between diabetes and cancer, including colorectal (4), breast (5), endometrial (6), and pancreatic (7) malignancies. Several biologically plausible mechanisms could explain this relationship. In particular, hyperinsulinemia, which occurs in patients with impaired fasting glucose and early type 2 diabetes, may affect the development of cancer directly or through insulin-like growth factor or stimulation of insulin-like growth factor receptors (8,9). Conversely, other studies of diabetes and cancer (10,11) have reported no or decreased risk (12,13), and reduced life expectancy as a result of diabetes itself may bring down the incidence of lung cancer that occurs more frequently in later life.

A comparative study (14) of lung cancer in diabetes, adjusting for smoking, reported a slight nonsignificant increased risk in women but not men. No incidence figures were given. Other studies (15–18) did not adjust for smoking, the major risk factor for lung cancer, and are therefore difficult to interpret. We estimated the incidence of lung cancer in a cohort of diabetic patients and investigated the hypothesis that the rate of lung cancer is different in diabetic compared with nondiabetic patients.

RESEARCH DESIGN AND METHODS

Diabetic patients and nondiabetic control subjects were identified from the General Practice Research Database (GPRD) (19,20), an observational database containing primary care records from throughout the U.K. Details of demographics, primary care diagnosis, and prescription treatment are routinely recorded against date in individual patient records. Information on referrals, secondary care diagnoses, and deaths are also captured because of the structure of the U.K. National Health Service, within which members of the general population are registered with a general practitioner and remain on the general practitioner's list while being treated by specialists or hospitalized. Major events from before computerization are added retrospectively. Medical events are automatically coded. Each patient within GPRD is assigned an up to standard (UTS) date when their records are considered to be of research standard.

The diabetes cohort included all patients on GPRD with a record of or a prescribed treatment (insulin or oral antidiabetic drug) for diabetes while permanently registered and with at least 1 year of computerized records after the UTS date. Potential control subjects had no record of diabetes or diabetic treatment on GPRD at any time and, at the diabetic patient's index date, were permanently registered, had at least 1 year of computerized records after the UTS date, and no history of lung cancer. These potential nondiabetic control subejcts were stratified by primary care practice, year of birth, and sex, and up to four control subjects were randomly selected from the ap-

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Abbreviations: GPRD, General Practice Research Database; UTS, up to standard.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

propriate stratum for each diabetic patient. When four control subjects were not available, the age band was widened by ±1 year to a maximum of ±5 years. Control subjects were only used once and had the same index date as that of the diabetic patient. Diabetic patients with no control subject, gestational diabetes, an incomplete index date, or a record of lung cancer on or before the index date were excluded. The observation period for each subject was from the index date to an end date. The primary end date allowed observation for the longest available period and was the first of the following: first record of lung cancer, death, transfer out of the practice, or the date of the final data collection. An additional end date was assigned to test the robustness of the results. The group end date was the earliest of the individual end dates for the four observations within each diabetic-control group and provided a censoring of observation to investigate the possibility that shorter life expectancy in diabetes may reduce the rate of lung cancer.

The diabetes cohort and nondiabetic control subjects were grouped into four smoking categories based on GPRD records in the 10 years before their end date: unknown (no record of smoking status), nonsmoker (non- or ex-smokers who had no record of being a smoker in the 10 years), smoker (a record of being a smoker but no record of being a non- or ex-smoker), or mixed status (records of being both a smoker and a nonsmoker). The proportion of current smokers on GPRD is consistent with the U.K. general household survey, but ex-smokers are underestimated, and it is presumed that ex-smokers have been classified for current medical purposes as nonsmokers (21). Smoking classification was based on the previous 10 years of records, as the risk of lung cancer falls after smoking cessation (22).

In addition, as biguanides are the only type 2 diabetes treatment that do not increase plasma insulin levels, the cohort was grouped by GPRD prescription record at anytime: no diabetic drug treatment, insulin only, biguanide only, other oral treatment only, biguanide plus another treatment, and insulin plus oral nonbiguanide. Separately, the diabetic patients were stratified into incident and nonincident diabetic cases. Incident cases had their first diabetes record (diagnosis or treatment) dated more than 1 year after the UTS date and provided a subgroup followed from diagnosis. The index date was the date of the first diabetes record for incident cases and the UTS date plus 1 year for others.

Diabetic patient and nondiabetic control records covering the observation period were searched for terms indicating lung cancer: tumors of the lung, trachea, pleura, bronchus, alveolar and respiratory tract, malignant pleural effusion and morphology, and procedures suggesting lung cancer. The general practitioner of each subject with one of these terms in their record was contacted and asked to send either copies of documentation related to the diagnosis or details that would allow the death certificate to be obtained. From this documentation, it was judged whether lung cancer had been diagnosed and if the tumor was primary or secondary metastatic to the lung. Primary tumors of the lung and bronchus were considered to be cases. Primary mediastinal tumors, mesothelioma, and sarcoma of the pleura were not considered to be cases. Retrieval of documents was through a third party to maintain confidentiality. From the documentation retrieved, each term was assigned a positive predictive value for lung cancer and where documentation was not available or was inconclusive, the cases were assigned as primary lung cancer or not based on the positive predictive value of the term used on GPRD.

Analysis

The observation period and incidence of primary lung cancer were calculated in the cohort, control subjects, and subgroups. Subjects with any lung cancer were censored at the date of the first record. For treatment groups, the date of the first prescription in the total observation period was the index date, and age, smoking categories, and numbers of lung cancer were recalculated. Comparisons in the risk of lung cancer between diabetic patients and nondiabetic control subjects used multivariable Cox regression to analyze the time to event or survival times, adjusting for age, sex, and smoking and using robust estimator of the variance to take account of potential clustering due to matching (23). Age was that on the index date if the patient had been born on 30 June of the year of birth, as GPRD only contains year of birth. Smoking categories, observation period, treatment groups, and cases of lung cancer were recalculated using the group end date, and the analysis repeated. The comparison was also repeated with all diabetic patients in the unknown smoking category artificially reassigned as nonsmokers. Comparative analyses were conducted using Stata (version 7.0; Stata, College Station, TX).

RESULTS — Between June 1987 and September 2000, 309 practices provided records on 66,848 diabetic patients (28,106 incident cases) and 267,272 nondiabetic control subjects, a ratio of 1:3.998. Individual practices provided data for a mean of 8.5 years (range 2.7–12.6 years). For diabetic patients, the average age at index date was 60.7 ± 17.3 (SD) years, 47.0% were women, and mean follow-up was 3.95 years compared with age at index 60.7 ± 17.3 years, 47.0% women, and 4.08 years follow-up in the nondiabetic control subjects. The 28,106 diabetic patients followed from diagnosis had a mean age of 61.1 ± 16.6 years, were 46.9% women, and had 2.99 years observation.

Initially, using all terms, 3,010 possible cases of lung cancer were identified. Sufficient documentation was received from 1993 cases (66.2%) to validate the diagnosis. From this documentation, 1,801 cases of primary lung cancer were confirmed. The terms suspected lung cancer, broncho-alveolar cancer, lung cancer, pancoast tumor, small-cell/oat-cell cancer, and neoplasm uncertain behavior lung had positive predictive values for primary lung cancer between 0.75 and 1. Patients with one of these terms in their record but without validation documentation were therefore accepted as cases ($n = 871$). The terms pleural cancer, malignant pleural effusion, secondary lung cancer, carcinoid, mesothelioma, and history of lung cancer had positive predictive values of ≤0.33; patients with a record of these terms but no documentation were not accepted as cases ($n = 146$). Overall, 90% of those with and 86% of those without validation documents were accepted as cases. A further thirteen cases of primary lung cancer were excluded because the date of the event was incomplete or outside the observation period. Therefore 2,659 cases of incident primary lung cancer were included in the analysis, 430 in the diabetes cohort, 2,229 in nondiabetic control subjects, and 172 in those with incident diabetes. The incidence of lung

Table 1—*The number of cases and incidences of primary lung cancer per 1,000 person-years by age and sex*

	All women with diabetes		All men with diabetes		All female control subjects		All male control subjects	
Age (years)	*n*	Incidence	*n*	Incidence	*n*	Incidence	*n*	Incidence
All ages	123	1.00 (0.84–1.20)	307	2.17 (1.94–2.43)	669	1.30 (1.21–1.41)	1,560	2.70 (2.57–2.84)
0–34	0	0	0	0	0	0	0	0
35–44	2	0.22 (0.06–0.89)	2	0.15 (0.04–0.61)	4	0.11 (0.04–0.30)	5	0.10 (0.04–0.23)
45–54	5	0.33 (0.14–0.78)	16	0.65 (0.40–1.07)	31	0.51 (0.36–0.72)	54	0.55 (0.42–0.72)
55–64	30	1.08 (0.75–1.54)	69	1.81 (1.43–2.29)	155	1.37 (1.17–1.60)	350	2.26 (2.04–2.51)
65–74	47	1.49 (1.12–1.98)	125	3.60 (3.02–4.29)	283	2.09 (1.86–2.34)	687	4.79 (4.45–5.17)
75–84	33	1.51 (1.08–2.13)	84	5.37 (4.33–6.65)	173	1.76 (1.51–2.04)	423	6.22 (5.65–6.84)
85–94	6	1.35 (0.61–3.01)	11	5.94 (0.29–10.72)	23	1.13 (0.75–1.70)	41	5.06 (3.72–6.87)
>95	0	0	0	0	0	0	0	0

Data are hazard ratio (95% CI) or *n*.

cancer was 1.63 (95% CI 1.48–1.79), 2.04 (1.96–2.13), and 2.05 (1.76–2.38) per 1,000 person-years in all diabetic patients, nondiabetic control subjects, and incident diabetic patients, respectively. Incidence was higher in men and increased with age (Table 1). Mean age at primary lung cancer was 72.9 years, with 29.8% women. Smoking status was recorded in 84.5% of the diabetes cohort (22.5% were either a smoker or mixed status and 62.0% were nonsmokers) and 73.4% of nondiabetic control subjects (21.2% were either smoker or mixed status and 52.2% were nonsmokers).

Compared with control subjects, using the primary end date adjusted for age, sex, and smoking category, the hazard ratio was 0.88 (95% CI 0.79–0.98) in total, 0.88 (0.73–1.07) in women, 0.88 (0.78–1.00) in men, and 1.12 (0.95–1.34) in incident diabetes. The hazard ratio was 0.98 (0.84–1.13) when observation was truncated using the group end date. When diabetic patients with unknown smoking status were artificially reassigned as nonsmokers, the hazard ratio was 0.92 (0.82–1.02) using the primary end date. Table 2 reports the description of subgroups, incidence of lung cancer, and comparative analysis after stratification by treatment group. An inverse association was found for those who received a prescription for both a biguanide and another treatment, but when observation was truncated to allow for shorter life expectancy no association was found with any treatment group. The median years of observation by age and diabetes status for subjects without lung cancer are given in Table 3.

CONCLUSIONS — Our large U.K. study estimated an incidence of primary lung cancer in all diabetic patients of 1.63 per 1,000 patient-years and provides evidence to suggest that while this is lower than the rate in the general population, the difference may be at least partly due to decreased life expectancy in diabetes. This inverse association was seen when all subjects were followed for their longest possible period of observation. Life expectancy could not be adjusted for directly because of the limitations of the data source, but when the observation periods within each cohort-control group were equal, the association was no longer seen. In addition to the slightly shorter median period of observation found in older diabetic patients, this finding suggests that the shorter life expectancy in diabetes results in less opportunity for lung cancer, which has a peak incidence in the eighth decade of life (24). The diabetic patients may be less likely to survive to have an effect of cigarette smoking on their lungs, particularly as smoking amplifies the excess coronary risk of type 2 diabetes (25).

When the rate of lung cancer in diabetic patients followed from diagnosis

Table 2—*Treatment categories: description, incidence of lung cancer, and comparison with nondiabetic control subjects by observation period*

Treatment group	Patients *n* (% total)	Age (mean ± SD)	Mean years observation*	Lung cancer (*n*)*	Incidence† (95% CI)	Comparison with nondiabetic control subjects [total number of cases, hazard ratio (95% CI)] Primary end date‡	Group end date‡
No drug treatment	13,330 (19.9)	64.7 ± 14.7	2.9	111	2.91 (2.42–3.51)	520, 1.22 (0.99–1.52)	394, 1.00 (0.77–1.31)
Biguanides only	4,852 (7.3)	60.4 ± 13.4	2.4	21	1.77 (1.15–2.71)	150, 0.97 (0.61–1.55)	86, 1.32 (0.76–2.29)
Insulin only	11,628 (17.4)	42.9 ± 21.1	4.2	36	0.72 (0.52–0.99)	230, 0.94 (0.66–1.35)	90, 1.02 (0.60–1.73)
Biguanides + any other treatment	17,727 (26.5)	62.2 ± 12.5	4.7	96	1.16 (0.95–1.41)	788, 0.63 (0.51–0.79)	222, 1.14 (0.82–1.60)
Oral treatment only (not biguanides)	17,400 (26.0)	68.5 ± 12.7	2.9	152	3.02 (2.58–3.55)	879, 1.16 (0.97–1.39)	457, 1.13 (0.89–1.43)
Insulin + oral nonbiguanide	1,911 (2.9)	60.0 ± 16.6	4.5	13	1.53 (0.89–2.63)	91, 0.76 (0.42–1.38)	30, 1.24 (0.53–2.91)
All diabetic patients	66,848	60.8 ± 17.3	3.9	430	1.63 (1.48–1.79)	2,659, 0.88 (0.79–0.98)	1,280, 0.98 (0.84–1.13)

*From date of first prescription for those in prescription treatment groups and from date of first diagnosis for others; †incidence of lung cancer per 1,000 person-years using primary end date; ‡multivariable Cox regression with the nondiabetic control subjects as the baseline, adjusting for age, sex, and smoking.

Table 3—*The median years of observation by age at index date for subjects without lung cancer*

Age-group (years)	All diabetes	Control subjects
0–54	3.96 (20,727)	3.89 (82,894)
55–64	4.15 (15,142)	4.25 (60,452)
65–74	3.69 (16,527)	3.93 (65,836)
≥75	2.59 (14,022)	3.02 (55,861)

Data are median (*n*).

was compared with their nondiabetic control subjects, no significant difference was identified. A higher rate of lung cancer in those newly diagnosed could be because they are less likely to have developed complications with the resultant shorter life expectancy or alternatively may be the result of changes in carbohydrate metabolism due to a latent tumor (8) or possibly a detection bias from greater general contact with medical care or from screening. If the difference in incidence is due to shortening of life expectancy or altered carbohydrate metabolism, then the true incidence of lung cancer in diabetes will vary with time from diagnosis.

Underadjustment for smoking status could also contribute to an inverse association between diabetes and lung cancer. A bias in recording was detected, with more diabetic patients having at least one smoking record compared with nondiabetic control subjects. Physicians have more opportunity and perhaps more incentive to counsel diabetic patients against smoking. If these factors resulted in diabetic patients with unclassified smoking status, being more likely than nondiabetic control subjects to be incorrectly treated as smokers or mixed status in the adjusted analysis, then the hazard ratio could be understated. However, two findings argue against this being the total explanation. Firstly, a bias in smoking recording would also be present in the truncated analysis where no inverse association was observed. Secondly, artificial reclassification of all diabetic patients with unknown smoking status as nonsmokers resulted in only a marginal increase in the hazard ratio. Variables such as type of smoking, tar content, age at starting, and duration can also influence the risk of lung cancer (22), and a dose relationship between diabetes and cigarette smoking has been reported (26). We did not have data to account for these variables, but, again, residual confounding would have affected the analysis with the group end date. However, it is possible that differences in smoking habits between the diabetes cohort and nondiabetic control subjects have not been fully adjusted given the limitations of observational data. The percentage of smokers among nondiabetic control subjects with known status is slightly less than national figures for regular cigarette smoking (1994–1999) (27), 24% compared with 27%, respectively. The difference may be due to our "mixed" category.

As hyperinsulinemia in impaired fasting glucose and early type 2 diabetes may affect the development of cancer (8,9) and biguanides are the only treatment for type 2 diabetes that do not increase plasma insulin levels, (28) we also looked at lung cancer by diabetic treatment. Patients with type 1 diabetes would be included in the insulin group, so all other groups would include only patients with type 2 diabetes. While the incidence of lung cancer did vary between the treatment groups in general, higher incidence was found with greater mean age. No increased risk of lung cancer was seen in any group, and the inverse association found in those who received a biguanide plus another treatment no longer existed when the observation period was truncated to account for differences in life expectancy.

The previous study (14) that reported a small nonsignificant increased risk of lung cancer in diabetic women but not men adjusted for multiple variables in the analysis, including current and former smoker, BMI, recreational activity, income, and alcohol consumption and may have accounted for life expectancy to some degree. Our hazard ratio was the same for men and women. Many but not all observational studies of other specific cancers in diabetes have found positive associations. If these increased risks are true, then our converse finding may be due to the effects of smoking on both cardiovascular risk and lung cancer or that lung cancer occurs at a later age than many other cancers, giving time for the effects of diabetes on the cardiovascular system. Prostate cancer, a malignancy of older men, is reported to decrease with duration of diabetes (13,29); however, the reverse trend has also been reported (30). Alternatively, as the diabetes-cancer relationship is not fully understood, any association may vary with tumor type (9,31).

In conclusion, no increased risk of lung cancer in diabetic patients was found in a large U.K. retrospective study and the lower incidence may be due to shorter life expectancy. The incidence of lung cancer in diabetes may therefore vary depending on time from diagnosis.

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