Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies

R Huxley*,1, A Ansary-Moghaddam1, A Berrington de González2, F Barzi1 and M Woodward1

The George Institute for International Health, The University of Sydney, PO Box M201, Missenden Road, Sydney NSW 2050, Australia; 2Cancer Research UK Epidemiology Unit, University of Oxford, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, UK

Pancreatic cancer is the eighth major form of cancer-related death worldwide, causing 227 000 deaths annually. Type-II diabetes is widely considered to be associated with pancreatic cancer, but whether this represents a causal or consequential association is unclear. We conducted a meta-analysis to examine this association. A computer-based literature search from 1966 to 2005 yielded 17 case–control and 19 cohort or nested case–control studies with information on 9220 individuals with pancreatic cancer. The age and sex-adjusted odds ratio (OR) for pancreatic cancer associated with type-II diabetes was obtained from each study. The combined summary odds ratio was 1.82 (95% confidence interval (95% CI) 1.66–1.89), with evidence of heterogeneity across the studies (P = 0.002 for case–control and P = 0.05 for cohort studies) that was explained, in part, by higher risks being reported by smaller studies and studies that reported before 2000. Individuals in whom diabetes had only recently been diagnosed (< 4 years) had a 50% greater risk of the malignancy compared with individuals who had diabetes for ≥ 5 years (OR 2.1 vs 1.5; P = 0.005). These results support a modest causal association between type-II diabetes and pancreatic cancer.

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 MATERIALS AND METHODS

Data sources

Relevant studies were identified through EMBASE, PUBMED and MEDLINE using a combined text word and MESH heading search strategy of pancreatic cancer (pancreas, tumour, malignancy) and type-II diabetes (NIDDM, diabetes, adult-onset diabetes). References from identified studies, as well as from the previous review, were also scanned to identify any other relevant studies.

Study selection and data synthesis

Studies were included in this systematic review if they had published quantitative estimates and standard errors, or confidence limits, of the association between type-II diabetes and pancreatic cancer by January 2005. Studies were excluded if they provided only an estimate of effect, with no means by which to calculate the standard error, or if the estimates were not adjusted by age. The variance of the log odds ratio (OR) from each study was calculated by converting the 95% confidence interval (CI) to its natural logarithm by taking the width of the CI and dividing by 3.92. If the variance was unavailable, P-values were used to estimate the CI. Some studies provided more than one OR according to the duration of diabetes before being diagnosed with pancreatic cancer. To maintain consistency across studies, the ORs for individuals diagnosed with diabetes > 1 year prior to the diagnosis of pancreatic cancer were extracted and combined. Summary estimates were obtained separately for case–control and cohort studies by means of a ‘random effects’ approach and studies...
were weighted according to an estimate of its 'statistical size' defined as the inverse of the variance of the log OR (Woodward, 2005). In addition, studies that reported separate ORs for mutually exclusive categories of duration since diabetes was diagnosed (e.g. 1–4 years, 5–9 years, >10 years) were pooled separately to examine how the strength of the association varied with duration of diabetes. Possible sources of heterogeneity were investigated by comparing the results for studies combined with respect to particular characteristics (e.g. sex, method of diagnosis of diabetes). All analyses were performed using STATA, version 8.

RESULTS

A total of 17 case–control and 19 cohort or nested case–control studies with information on a total of 9220 individuals with pancreatic cancer had published estimates of the association between diabetes and the malignancy. Six additional studies were excluded from this review; one study had published the standardised mortality ratio only (Kessler, 1970), and the remaining five studies contained duplicate information (La Vecchia et al, 1990; Davey Smith et al, 1992; Calle et al, 1998; Silverman et al, 1999; La Coughlin et al, 2000). The summary characteristics of included studies are shown in Tables 1 and 2. The majority of the study populations were from either North America (n = 16) or Europe (n = 14) with the remaining five studies from either Australasia or South America. With the exception of one study that had recorded diagnosis of diabetes by proxy, diagnosis of diabetes was either through self-report, an oral glucose-tolerance test, medical records or a combination of these three methods.

The pooled OR for case–control studies was 1.94 (95% CI 1.53–2.46) (Figure 1), this being nonsignificantly higher than the summary estimate from cohort studies: 1.73 (1.59–1.88; Figure 2) (P for heterogeneity = 0.37). The combined estimate from all studies was 1.82 (95% CI 1.66–1.99). There was some evidence of

Table 1  Case–control studies of diabetes and pancreatic cancer

| First author and year | PC cases | Controls | Diabetes | % PC cases | Level of adjustment | Relative risk | 95% CI |
|----------------------|----------|----------|----------|------------|---------------------|--------------|--------|
| Cuzick, 1989         | 216      | 279      | SR, MR   | >1         | 6.0 M               | Age, sex     | 2.59   | 0.63–16.1 |
| Wynder, 1973         | 142      | 142      | SR       | >2         | 2.0 F               | Age, sex, race, hospital | 6.64 | 1.33–65.2 |
| Norell, 1986         | 99       | 301      | SR       | >5         | 16.7 F              | Age, sex, residence | 7.80 | 1.90–38.5 |
| Frye, 2000           | 116      | 232      | MR       | >1         | 4.0 F               | Age, sex     | 2.40   | 0.60–9.70 |
| Farrow, 1990         | 148      | 188      | P        | >3         | 7.1 F               | Age, smoking, education | 1.75 | 0.46–7.09 |
| Jain, 1991           | 249      | 505      | SR, P    | 5–10       | 3.8 F               | Age, sex, smoking, energy and fiber intake | 2.14 | 0.75–6.17 |
| Lin, 1981            | 109      | 109      | SR       | >1         | 7.4 F               | Age, sex, race, marital status, hospital | 0.78   | 0.28–2.09 |
| Bueno de Mesquita, 1992 | 176    | 487      | SR, P    | >1         | 6.4 M               | Age, proxy, smoking | 0.73 | 0.27–2.00 |
| Eke, 1992            | 179      | 239      | SR       | >1         | 7.3 F               | Age, sex, smoking, education | 0.93 | 0.35–2.50 |
| Kalapothaki, 1993    | 181      | 362      | SR       | >10        | 5.0 F               | Age, sex, hospital | 3.60 | 1.04–7.10 |
| Silverman, 2001      | 526      | 2153     | SR, P    | 2–4        | NA                  | Age, sex, race, area, smoking, alcohol, BMI | 1.40 | 0.70–2.40 |
| Gold, 1985           | 201      | 402      | SR, P    | >2         | 10.0 F              | Age, sex, race, hospital, BMI | 0.63 | 0.34–1.15 |
| La Vecchia, 1994     | 362      | 1089     | SR       | >1         | 14.4 M              | Age, sex, education, BMI | 2.60 | 1.80–4.80 |
| Bonelli, 2003        | 202      | 406      | SR       | >1         | 9.8 F               | Age, sex, centre, education, occupation, tobacco, alcohol | 1.40 | 0.80–2.50 |
| Lee, 1996            | 282      | 282      | SR       | >1         | 28.7 F              | Age, sex, smoking, alcohol | 2.84 | 1.80–4.52 |
| Gullo, 1994          | 720      | 720      | SR, MR   | >1         | 13.6 F              | Age, social class, region, hospital | 1.80 | 1.30–2.50 |
| O'Mara, 1985         | 93       | NA       | SR       | NA         | 7.6 F               | Age | 2.40 | 1.80–3.50 |

PC = pancreatic cancer; SR = self-reported diabetes; MR = medical record of diabetes; P = proxy provided information on diabetes status; NA = data not available.
heterogeneity within both the case–control \((P = 0.002)\) and the cohort studies \((P = 0.05)\) that was that was not explained by differences in strength of effect between men and women, adjustment for cigarette smoking or the method of diagnosis of diabetes \((\text{Figure 3})\). Furthermore, there was no difference in the summary RR from those studies that had adjusted for variables other than age and sex compared to those studies that were unable to adjust for other potential confounders \((R R 1.85 \text{ vs } 1.80;\)
DISCUSSION

The findings from this review suggest that earlier reports of a more than two-fold excess risk of pancreatic cancer among individuals with type-II diabetes are likely to have overestimated the strength of the association (Ragozzino et al, 1982; Friedman and Van Den Eeden, 1993; Everhart and Wright, 1995). Although the current data suggest an 80% greater risk of pancreatic cancer among individuals with type-II diabetes, even this may be an exaggeration of the true strength of the relationship, as it does not consider the considerable potential for reverse causality.

The RR of pancreatic cancer was demonstrated to be negatively associated with the duration of diabetes. Among individuals with a long history of diabetes (>5 years), the excess RR of pancreatic cancer was about 50% lower than in individuals for whom the duration of diabetes was shorter (RR 1.5 vs 2.1; P = 0.005). This supports the hypothesis that, in some cases, diabetes may be an early manifestation of the tumour, as otherwise the RR would be expected to increase, rather than decrease, with duration of diabetes. In an earlier review similar RRs of pancreatic cancer by duration of diabetes were reported (Everhart and Wright, 1995) but, the categories for duration of diabetes, unlike in the current meta-analysis, were not mutually exclusive (i.e. >5 years diabetes duration was a subset of the >1 year group) and therefore, the RR for the >1 year duration of diabetes was likely to have been diluted by the inclusion of cases with a longer history of diabetes (and hence a smaller RR).

Evidence from the literature further supports the hypothesis that pancreatic cancer can induce a diabetic state. First, several studies have shown that the risk of pancreatic cancer among individuals with diabetes is lessened after exclusion of those with less than 1 year diabetes (Ragozzino et al, 1982; Cuzick and Babiker, 1989). Second, in studies among individuals with pancreatic cancer who underwent tumour resection, insulin sensitivity and diabetes status...
were reported as showing substantial improvement 3 months after surgery (Permert et al, 1993). And third, molecular studies of sera from pancreatic cancer patients have identified peptides that are suggested to be diabetogenic (Wang et al, 2003).

Confounding is also likely to have been present since diabetes and pancreatic cancer. However, the exclusion of any small negative studies is unlikely to have materially altered the overall summary estimate. There was some evidence to suggest that there was some possibility of publication bias that may have resulted in an underestimation of the overall association, since it has been slightly underestimated the overall association, since it has been reported that Type-1 diabetes is not associated with pancreatic cancer (Zendehdel et al, 2003). The literature, however, regarding cancer mortality among individuals with type 1 diabetes, is limited by small sample size and short length of follow-up (Mihara et al, 1986; Martinenghi et al, 1997) and therefore do not preclude a

Figure 2 Relationship between type-II diabetes and risk of pancreatic cancer in cohort studies (conventions as in Figure 1).
possible association. However, it is likely that the substantial majority of individuals with diabetes included in these studies had type-II diabetes, since this is by far the most common form particularly in older individuals. Additional limitations of this review include the reliance, in the large majority of studies, on self-reported diabetes and the potential for misclassification on death certificates of site-specific cancers, although the sensitivity analyses did not show any difference in the risk between those studies that used self-reported diabetes compared with those that diagnosed diabetes either through medical records or by an oral glucose tolerance test.

To date, only cigarette smoking, and possibly obesity, has been identified as being causally associated with pancreatic cancer. The evidence from this review indicates that type-II diabetes is likely to be a third modifiable risk factor (Knowler et al., 2002; Davey Smith et al., 2005) and unless the increasing worldwide prevalence of all three risk factors is halted, the incidence of pancreatic cancer will rise substantially within the next couple of decades.

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