Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study

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Raised risks of several cancers have been found in patients with type II diabetes, but there are few data on cancer risk in type I diabetes. We conducted a cohort study of 28,900 UK patients with insulin-treated diabetes followed for 520,517 person-years, and compared their cancer incidence and mortality with national expectations. To analyse by diabetes type, we examined risks separately in 23,834 patients diagnosed with diabetes under the age of 30 years, who will almost all have had type I diabetes, and 5066 patients diagnosed at ages 30–49 years, who probably mainly had type II. Relative risks of cancer overall were close to unity, but ovarian cancer risk was highly significantly raised in patients with diabetes diagnosed under age 30 years (standardised incidence ratio (SIR) = 2.14; 95% confidence interval (CI) 1.22–3.48; standardised mortality ratio (SMR) = 2.90; 95% CI 1.45–5.19), with greatest risks for those with diabetes diagnosed at ages 10–19 years. Risks of cancer at other major sites were not substantially raised for type I patients. The excesses of obesity- and alcohol-related cancers in type II diabetes may be due to confounding rather than diabetes per se.

Keywords: insulin-treated diabetes; cohort

Diabetes mellitus is the most common metabolic abnormality in Western populations. It occurs through two different primary disease processes, type I (insulin-dependent) and type II (non-insulin dependent), with different patient characteristics. The metabolic and hormonal antecedents and consequences of diabetes, and the treatments for it, might affect the risk of cancer. Most studies of cancer risks in patients with diabetes have related to type II diabetes. Raised risks have been found, although not entirely consistently, for endometrial, breast, renal, gallbladder and liver cancers (Kessler, 1970; Armstrong et al., 1976; Ragozzino et al., 1982; Green and Jensen, 1985; O’Mara et al., 1985; Adami et al., 1991; La Vecchia et al., 1994; Hjalgrim et al., 1997; Wideroff et al., 1997; Verlato et al., 2003), but interpretation is uncertain because of potential confounding by obesity and alcohol consumption. Pancreatic cancer risk has been found raised (Everhart and Wright, 1995), but there is uncertainty about the direction of causation, because pancreatic cancer can cause diabetes.

The aetiology of type I diabetes is not related to obesity or alcohol use, and the diabetes generally occurs well before the ages at which pancreatic cancer is prevalent. The only studies of cancer risk in patients with type I diabetes, however, have been relatively small – cohorts totalling 2400 patients (Hjalgrim et al., 1997) and a few case–control data (O’Mara et al., 1985) – and hence of limited power. Analyses of cancer risk by duration since diagnosis of diabetes could potentially illuminate causality, but cohort analyses of this factor have only been conducted for 1500 patients (Hjalgrim et al., 1997). We examined cancer risks in a UK cohort of 28,900 patients with insulin-treated diabetes of known date of diagnosis, most aged under 30 years at diagnosis of diabetes and therefore probably with type I diabetes.

MATERIALS AND METHODS

The Diabetes UK (formerly British Diabetic Association (BDA)) cohort consists of 28,900 UK resident patients with insulin-treated diabetes who were under age 50 years at diagnosis of this disease. A total of 12,893 were identified in a national register of childhood cases assembled by the BDA from 1972 to 1986, and the rest were recorded in population-based geographical registers for various parts of the UK during 1972–1995, varying in their dates of data collection and the ages at diagnosis that were included. Details of the registers can be found in Laing et al. (1999).
RESULTS

A total of 29701 patients with insulin-treated diabetes diagnosed under age 50 years were identified in the component registers of the study, of whom 27 were excluded because diabetes was secondary to a congenital disease (largely cystic fibrosis), 35 because of faulty or incomplete data at registration and 334 because it was unknown whether diagnosis was at ages under 30 or 30–49 years. Of the remaining 405 (1.4%) patients, could not be traced at the NHSCRs and CSA, and the remaining 28900 formed the study cohort. A total of 23834 of the patients were diagnosed at ages under 30 years, and 5066 at ages 30–49 years (Table 1); 15085 were diagnosed before 1980, 13715 later and 100 at an unspecified date; 15688 were male and 13212 female subjects.

During follow-up there were 3861 deaths, 221 losses to follow-up through emigration or otherwise leaving the National Health Service, 88 patients whose follow-up was censored when they reached age 85 years, and 24730 subjects who reached the end of follow-up alive under age 85 years; 20676 of these latter were still under age 50 years. Follow-up was for a total of 520517 person-years, an average of 18.0 person-years per subject. Of 2301 deaths in men, 228 were from cancer, and of 1560 in women, 150 were from cancer. In all, 582 cancer registrations other than nonmelanoma skin cancer were recorded in the cohort, 305 in men and 277 in women.

Table 2 shows cancer mortality in each sex in patients diagnosed with diabetes under age 30 years and in those diagnosed at 30–49 years. In the former group, there was a significant excess of deaths from cancer of the ovary (SMR 2.90; 95% CI 1.45–5.19), but not of any other cancer, including cancer of the pancreas (SMR 0.91; 95% CI 0.25–2.32). In the patients diagnosed with diabetes at ages 30–49 years, there was no raised risk of ovarian cancer (P = 0.016 compared with the risk in the younger-onset diabetes patients), but there was a significant decrease in deaths from cancer of the nervous system (SMR 0.25; 95% CI 0.03–0.91) and nonsignificantly raised risks for several tumours previously reported at raised risk in patients with diabetes – cancers of the corpus uteri, pancreas, gall bladder and kidney (although not liver cancer). Subdividing the ovarian cancer risk more finely by age at onset of

| Age at diagnosis of diabetes (years) | Male | Female | Total |
|-------------------------------------|------|--------|-------|
| 0–14                                | 9503 | 8818   | 18321 |
| 15–29                               | 3184 | 2229   | 5413  |
| 30–49                               | 2944 | 2122   | 5066  |

| Year of diagnosis of diabetes*       |      |        |      |
|--------------------------------------|------|--------|------|
| < 1960                               | 681  | 575    | 1256 |
| 1960–1969                            | 1212 | 1027   | 2239 |
| 1970–1979                            | 6272 | 5318   | 11590|
| 1980–1989                            | 6150 | 5131   | 11281|
| ≥ 1990                              | 1316 | 1118   | 2434 |

| Country of residence                 |      |        |      |
|--------------------------------------|------|--------|------|
| England and Wales                    | 9163 | 7852   | 17015|
| Scotland                             | 6041 | 4860   | 10901|
| Northern Ireland                     | 484  | 500    | 984  |

| Year of entry to cohort              |      |        |      |
|--------------------------------------|------|--------|------|
| 1972–1979                            | 4147 | 3684   | 7831 |
| 1980–1989                            | 7307 | 6077   | 13384|
| 1990–1993                            | 4234 | 3451   | 7685 |

| Total                                | 15688| 13212  | 28900|

*Omitting 100 patients diagnosed under age 30 years, for whom the exact age and year of diagnosis is not known.
diabetes, relative risks were 2.25 (95% CI 0.06–12.52) for subjects with diabetes incident under age 10 years, 4.56 (95% CI 1.67–9.92; \( P = 0.005 \)) for diabetes at ages 10–19 years and 1.94 (95% CI 0.53–4.97) for diabetes at ages 20–29 years (not in table).

Incidence of ovarian cancer was also significantly increased in patients with diabetes of onset under age 30 years (Table 3), but there were not significantly raised or diminished SIRs for any other cancer site in this age group. Similarly to the mortality results, the SIR was greatest for those with diabetes incident at ages 10–19 years (SIR 2.90; 95% CI 1.32–5.50; \( P = 0.01 \)). The histological types of the 16 ovarian cancers occurring in this age group were six cystic, mucinous or serous, two germ cell, two adenocarcinomas, one granulosa cell, one Brenner cell and four unspecified cancers. In patients with diabetes incident at ages 30–49 years, there was significantly reduced incidence of prostate cancer and of nervous system cancer; all cases of the latter were gliomas. There was also a borderline significant excess of endometrial cancer in the same age group, but no raised risk of ovarian cancer (\( P = 0.018 \) compared with the risk in the younger-onset diabetes patients).

### Table 2  Cancer mortality risks by age at onset of diabetes: selected sites

| ICD9 code | Cancer site         | No. | SMR (95% CI)   | No. | SMR (95% CI)   |
|-----------|---------------------|-----|----------------|-----|----------------|
| 150       | Oesophagus          | 5   | 0.97 (0.31–2.26) | 15  | 1.15 (0.64–1.90) |
| 151       | Stomach             | 5   | 0.94 (0.31–2.20) | 9   | 0.66 (0.30–1.25) |
| 153–154   | Colon and rectum    | 6   | 0.52 (0.19–1.13) | 29  | 1.01 (0.67–1.44) |
| 155       | Liver               | 1   | 0.50 (0.21–2.79) | 4   | 1.01 (0.27–2.58) |
| 156       | Gall bladder        | 1   | 2.43 (0.06–13.52) | 2   | 1.81 (0.22–6.55) |
| 157       | Pancreas            | 4   | 0.91 (0.25–3.23) | 16  | 1.44 (0.82–2.33) |
| 162       | Lung                | 27  | 0.96 (0.63–1.39) | 67  | 0.84 (0.65–1.06) |
| 174, 175  | Breast              | 10  | 0.74 (0.36–1.37) | 17  | 0.86 (0.50–1.38) |
| 179, 182  | Corpus uteri        | 1   | 1.30 (0.03–7.26) | 4   | 2.13 (0.58–5.45) |
| 183       | Ovary               | 11  | 2.90 (1.45–5.19)** | 6   | 0.86 (0.32–1.87) |
| 185       | Prostate            | 1   | 0.30 (0.01–1.67) | 9   | 0.73 (0.33–1.38) |
| 188       | Bladder             | 2   | 0.80 (0.10–2.90) | 3   | 0.39 (0.08–1.14) |
| 189       | Kidney              | 1   | 0.34 (0.01–1.89) | 8   | 1.30 (0.56–2.56) |
| 191, 192  | Nervous system      | 7   | 0.78 (0.31–1.60) | 2   | 0.25 (0.03–0.91)* |
| 196–199   | Primary unknown     | 7   | 0.82 (0.33–1.69) | 23  | 1.12 (0.71–1.68) |
| 200, 202  | Non-Hodgkin’s lymphoma | 5    | 0.89 (0.29–2.08) | 10  | 1.35 (0.65–2.47) |
| 204–208   | Leukaemia           | 7   | 0.87 (0.35–1.80) | 8   | 1.46 (0.63–2.87) |
| 140–208   | All malignancies    | 123 | 0.90 (0.75–1.08) | 255 | 0.93 (0.82–1.05) |

ICD = International Classification of Diseases; SMR = standardised mortality ratio; CI = confidence interval. *\( P < 0.05 \). **\( P < 0.01 \).

### Table 3  Cancer incidence risks by age at onset of diabetes: selected sites

| ICD9 code | Cancer site         | No. | SIR (95% CI)   | No. | SIR (95% CI)   |
|-----------|---------------------|-----|----------------|-----|----------------|
| 150       | Oesophagus          | 4   | 1.06 (0.29–2.73) | 15  | 1.49 (0.83–2.46) |
| 151       | Stomach             | 7   | 1.20 (0.48–2.47) | 12  | 0.77 (0.40–1.35) |
| 153–154   | Colon and rectum    | 14  | 0.71 (0.39–1.19) | 52  | 1.11 (0.83–1.46) |
| 155       | Liver               | 1   | 0.70 (0.02–3.92) | 7   | 2.46 (0.99–5.07) |
| 156       | Gall bladder        | 0   | —              | 1   | 0.57 (0.01–3.19) |
| 157       | Pancreas            | 5   | 1.36 (0.44–3.18) | 12  | 1.30 (0.67–2.27) |
| 162       | Lung                | 27  | 1.14 (0.75–1.65) | 56  | 0.81 (0.61–1.05) |
| 172       | Melanoma            | 20  | 1.21 (0.74–1.86) | 9   | 1.20 (0.53–2.29) |
| 174, 175  | Breast              | 34  | 0.87 (0.60–1.21) | 41  | 0.87 (0.62–1.17) |
| 179, 182  | Corpus uteri        | 4   | 1.20 (0.33–3.08) | 12  | 1.84 (0.95–3.22) |
| 180       | Cervix              | 10  | 0.72 (0.34–1.32) | 7   | 1.48 (0.60–3.06) |
| 183       | Ovary               | 16  | 2.14 (1.22–3.48)** | 6   | 0.72 (0.26–1.57) |
| 185       | Prostate            | 6   | 0.84 (0.31–1.82) | 15  | 0.57 (0.12–0.94)* |
| 186       | Testis              | 13  | 0.93 (0.49–1.59) | 1   | 0.77 (0.02–4.27) |
| 188       | Bladder             | 7   | 0.91 (0.37–1.88) | 20  | 1.00 (0.61–1.55) |
| 189       | Kidney              | 2   | 0.43 (0.05–1.54) | 10  | 1.13 (0.54–2.08) |
| 191, 192  | Nervous system      | 14  | 1.02 (0.56–1.72) | 2   | 0.26 (0.03–0.94)* |
| 196–9     | Primary unknown     | 5   | 0.65 (0.21–1.51) | 15  | 0.81 (0.45–1.34) |
| 200, 202  | Non-Hodgkin’s lymphoma | 14    | 1.13 (0.62–1.89) | 12  | 1.00 (0.52–1.74) |
| 204–208   | Leukaemia           | 10  | 0.90 (0.43–1.65) | 5   | 0.69 (0.22–1.61) |
| 140–172, 174–208 | All malignancies except nonmelanoma skin cancer | 241 | 0.95 (0.84–1.08) | 341 | 0.95 (0.85–1.05) |

ICD = International Classification of Diseases; SIR = standardised incidence ratio; CI = confidence interval. *\( P < 0.05 \). **\( P < 0.01 \).
Diabetes diagnosed at ages < 30*  
| ICD9 code | Cancer site | No. | SMR | No. | SMR | No. | SMR | No. | SMR |
|------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|
| 162        | Lung        | 0   | 0   | 0   | 1.31| 6   | 0.90| 8   | 0.97|
| 174, 175   | Breast      | 0   | 1.50| 3   | 0.63| 3   | 0.87| 1   | 0.33|
| 183        | Ovary       | 0   | 2.16| 3   | 3.12| 0   | 0   | 7   | 6.01***|
| 140–208    | All malignancies | 9   | 0.92| 15  | 0.80| 30  | 1.02| 25  | 0.77| 43  | 0.95|

Diabetes diagnosed at ages 30 – 49*  
| ICD9 code | Cancer site | No. | SMR | No. | SMR | No. | SMR | No. | SMR |
|------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|
| 157        | Pancreas    | 2   | 3.14| 3   | 0.99| 7   | 1.61| 2   | 0.77|
| 162        | Lung        | 6   | 1.53| 21  | 1.00| 29  | 0.89| 11  | 0.58|
| 174, 175   | Breast      | 1   | 0.40| 6   | 0.88| 6   | 0.93| 3   | 0.92|
| 183        | Ovary       | 1   | 1.56| 3   | 1.30| 1   | 0.40| 1   | 0.78|
| 140–208    | All malignancies | 18  | 1.02| 72  | 0.97| 109 | 1.04| 45  | 0.77| 11  | 0.84|

*ICD = International Classification of Diseases; SMR = standardised mortality ratio. ***P < 0.001. *Person-years for the duration categories shown are 176,795, 174,854, 85,680, 14,650 and 6,883, respectively. One death in Table 2 not included here because exact duration since diagnosis is not known. Person-years for the duration categories shown are 15,036, 23,568, 15,218, 5,497 and 817, respectively. Trend in risk with duration significant, P = 0.01.

Examination of cancer risks by sex (not in table) did not show any consistent patterns except that the raised pancreatic cancer risk in patients with diabetes diagnosed at ages 30 – 49 years was limited to men (SMR 1.72; 95% CI 0.89 – 3.01. SIR 1.97; 95% CI 0.98 – 3.53), and the lung cancer deficit in the same age group was most pronounced in women (SMR 0.58; 95% CI 0.31 – 0.99. SIR 0.53; 95% CI 0.28 – 0.90; P = 0.02). With regard to sites for which sex differences in cancer relative risk in patients with diabetes have been reported in the literature, colorectal cancer, for which greater female SIRs or SMRs have been reported (Will et al, 1998), did not show consistently greater SIRs or SMRs in males, and renal cancer, for which greater female SIRs or SMRs have been reported (Lindblad et al, 1999), did not show greater SIRs or SMRs in female subjects. Analyses of breast cancer risk separately at attained ages under 50 years, and 50 years and above, as a proxy for premenopausal and postmenopausal ages, were hampered by small numbers, but gave no significant results and no indication of systematically different risks by menopausal status.

When cancer mortality risks were analysed by time since onset of diabetes (Table 4), there was no trend for cancers overall. All ovarian cancer deaths in women with diabetes diagnosed under age 50 years occurred more than 10 years after diabetes diagnosis, with the greatest excess beyond 40 years (SMR 6.0; 95% CI 2.4 – 12.4; P < 0.001). In the patients diagnosed with diabetes at ages 30 – 49 years, the modest excess of pancreatic cancer deaths did not reflect raised risk at any particular point in follow-up. Lung cancer mortality risks in patients with diabetes diagnosed at ages 30 – 49 years diminished significantly with longer follow-up, but this was not apparent, based on smaller numbers, for those with young-onset diabetes.

Analyses of cancer incidence risks by duration of diabetes were based on shorter follow-up (see Materials and Methods) and are therefore not shown. Lung cancer risks in patients diagnosed with diabetes at ages 30 – 49 years generally diminished with time, and all ovarian cancers in patients with diabetes diagnosed under age 50 years occurred more than 10 years after diabetes diagnosis.

**DISCUSSION**

The most striking, and unexpected, finding of our study was the highly significant excess of ovarian cancer in women with insulin-treated diabetes diagnosed at young ages (i.e. those who presumptively had type I diabetes). There are few previous data on this risk: a nonsignificant odds ratio of 2.0 based on two cases (O’Marra et al, 1985) and a relative risk of 0.6 based on one case (Weiderpass et al, 2002b). As in previous studies (Kessler, 1970; Ragozzino et al, 1982; O’Marra et al, 1985; Adami et al, 1991; La Vecchia et al, 1994; Adler et al, 1996; Wideroff et al, 1997; Weiderpass et al, 2002b), we did not find a raised risk of ovarian cancer in women with older onset (i.e. largely type II) diabetes. Ovarian cancer rates might be raised in patients with diabetes via effects of hyperinsulinaemia on the ovary (Adler et al, 1996), but such an effect (endogenous or exogenous) could apply to type II as well as type I diabetes. Raised IGF1 levels have been proposed as a mechanism (Weiderpass et al, 2002b), but bioavailable IGF1 is decreased in type I diabetes (Saukkonen et al, 2004). Shared environmental or genetic aetiological factors for type I diabetes and ovarian cancer could in principle be an explanation, but we know of no such factors. Chance is also a possibility.

It is a limitation that we do not have individual data on menstrual or reproductive factors in our cohort, but menstrual factors in studies of women with type I diabetes have been in a direction to give diminished, not raised, risk of ovarian cancer: episodes of amenorrhoea are more frequent in women with insulin-dependent diabetes than in women in general (Kjaer et al, 1992); menarche is delayed in women with diabetes incident under age 10 years (Kjaer et al, 1992); and limited evidence suggests that menopause is considerably younger in women with childhood onset type I diabetes (Dorman et al, 2001). Oral contraceptive (OC) use is protective against ovarian cancer (Weiss et al, 1996), and there is evidence that OC use is less common in patients with diabetes (Dorman et al, 2001), because of potential side effects. The expected effect on ovarian cancer risk would be too small, however, to explain our findings. It is unclear whether parity differs between women with type I diabetes and other women (Dorman et al, 2001), but the differences would need to be very large to explain our results. We know of no evidence on oophorectomy prevalence in women with diabetes. If it were reduced this could in principle raise ovarian cancer rates, but oophorectomy rates are too low in the UK (Swedlow et al, 2001) for this plausibly to explain the study findings.

There is inconclusive evidence that ovarian cancer risk may be increased by raised androgen levels (Risch, 1998), and serum androgen levels have been found raised in menstruating women with type I diabetes (Djursing et al, 1985). Free testosterone levels, however, are raised in women with type II diabetes (Andersson et al, 1993). It is not known whether androgen levels in women with type I diabetes have increased by raised androgen levels (Risch, 1998), and serum androgen levels have been found raised in menstruating women with type I diabetes (Djursing et al, 1985). Free testosterone levels, however, are raised in women with type II diabetes (Andersson et al, 1993).
et al, 1994). Polycystic ovary syndrome (PCO), which includes raised androgen levels, has been associated with increased risk of ovarian cancer (Schildkraut et al, 1996) and with type I diabetes (Escobar-Morreale et al, 2000). An association of PCO also exists, however, with type II (Rajkhowa et al, 2000).

Type I and type II diabetes differ greatly in mean age at onset, so the restriction of ovarian cancer risk to type I might be a consequence of hormonal factors acting specifically at puberty or reproductive ages. For instance, total and free serum testosterone levels are raised in late puberty in girls with type I diabetes (Meyer et al, 2000), but presumably would not be abnormal at puberty in women with type II diabetes, which is incident much later. We found greatest ovarian cancer risk for women with diabetes incident around pubertal ages.

Studies of predominantly type II diabetes patients have generally shown raised risks of endometrial, renal, gall bladder, liver and pancreatic cancers, inconsistently raised risks of breast and colorectal cancers and non-Hodgkin’s lymphoma, and diminished risk of prostate cancer (Kessler, 1970; Armstrong et al, 1976; Ragozzino et al, 1982; Green and Jensen, 1985; O’Mara et al, 1985; Adami et al, 1991, 1996; La Vecchia et al, 1994; Everhart and Wright, 1995; Zahm et al, 1995; Hjalgrim et al, 1997; Weiderpass et al, 1997, 2000, 2002a; Wideroff et al, 1997; Will et al, 1998; Lindblad et al, 1999; Verlato et al, 2003; Coker et al, 2004). Endometrial, postmenopausal breast, renal and less certainly gall bladder cancer risks have also been associated with obesity (International Agency for Research on Cancer, 2002), so the association of these cancers with type II diabetes might be a consequence of confounding by obesity. Oestrogen levels affect endometrial cancer risk (Grady and Ernster, 1996), but data are inconsistent on whether postmenopausal women with diabetes have raised oestrogen levels (Nyholm et al, 1989; Andersson et al, 1994). Possible mechanisms suggested for liver cancer in diabetes include alcohol consumption and hepatitis (Verlato et al, 2003). The reduced prostate cancer risk might relate to reduced testosterone levels (Andó et al, 1984).

Our data for patients aged 30–49 years, who primarily had type II diabetes, showed risks raised somewhat for endometrial, liver and pancreatic cancers, slightly for renal and colorectal cancers and not raised for gall bladder or breast cancers and NHL, with reduced risk of prostate cancer. We did not find appreciably raised risks of these tumours in patients with diabetes incident aged under 30 years, that is, largely type I. Type I diabetes aetiology, unlike type II, appears unconnected with obesity or alcohol. Previous data for type I diabetes have been based on very small numbers for endometrial, renal, pancreatic, breast and prostate cancers (O’Mara et al, 1985; Hjalgrim et al, 1997; Weiderpass et al, 2000) and absent for gall bladder and liver cancers. Although with uncertainty from wide confidence intervals, our data are compatible with the idea that the raised risk in type II diabetes for obesity- and alcohol-related tumours may reflect confounding by obesity and alcohol, rather than aetiology by diabetes per se.

The diminishing risks of lung cancer mortality with longer follow-up of our older-diagnosed diabetes patients may reflect selective survival of nonsmokers, given the very high cardiovascular mortality of older patients with diabetes. The few cohort studies that have published on nervous system cancer in patients with diabetes did not find decreased risk (O’Mara et al, 1985; Adami et al, 1991; Wideroff et al, 1997), so the significantly reduced risk in our patients with older-diagnosed diabetes may have been a chance finding, especially as there is no obvious mechanism. Brain tumour prevalence at autopsy has been found reduced in patients with diabetes, but the deficit was solely for glioma (Aronson and Aronson, 1965), whereas in our cohort all the brain tumours were gliomas.

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