Cancer Risk Among People With Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation

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OBJECTIVE
Evidence indicates an increased risk of certain cancers among people with type 2 diabetes. Evidence for rarer cancers and for type 1 diabetes is limited. We explored the excess risk of site-specific cancer incidence and mortality among people with type 1 and type 2 diabetes, compared with the general Australian population.

RESEARCH DESIGN AND METHODS
Registrants of a National Diabetes Registry (953,382) between 1997 and 2008 were linked to national death and cancer registries. Standardized incidence and mortality ratios (SIRs/SMRs) are reported.

RESULTS
For type 1 diabetes, significant elevated SIRs were observed for pancreas, liver, esophagus, colorectal (females only [F]), stomach (F), thyroid (F), brain (F), lung (F), endometrial, and ovarian, and melanoma and prostate (decreased risk). Significantly increased SMRs were observed for pancreas, liver, and kidney (males only), non-Hodgkin’s lymphoma, brain (F), and endometrium. For type 2 diabetes, significant SIRs were observed for almost all site-specific cancers, with highest SIRs observed for liver and pancreas, and decreased risks for prostate and melanoma. Significant SMRs were observed for liver, pancreas, kidney, Hodgkin’s lymphoma, gallbladder (F), stomach (F), and non-Hodgkin’s lymphoma (F). Cancer risk was significantly elevated throughout follow-up time but was higher in the first 3 months postregistration, suggesting the presence of detection bias and/or reverse causation.

CONCLUSIONS
Type 1 and type 2 diabetes are associated with an excess risk of incidence and mortality for overall and a number of site-specific cancers, and this is only partially explained by bias. We suggest that screening for cancers in diabetic patients is important.
There is now a large body of evidence indicating a strong and consistent increased risk of incident cancer associated with diabetes (1). For type 2 diabetes, the strength of the association depends on the specific cancer site, with the strongest relationships observed for liver and pancreatic cancers, followed by endometrial, postmenopausal breast, colorectal, bladder, non-Hodgkin’s lymphoma, and kidney cancer (2). For stomach cancer, there was an increased risk in a Japanese population (3), but it is not known if this extends to other populations, most of which have a much lower incidence of stomach cancer. The literature also consistently demonstrates a 10–20% decreased risk of prostate cancer among men with diabetes, due, in part, to the reduced levels of circulating testosterone levels in these individuals (4). For other, rarer malignancies, the number of studies is small, and more importantly, they usually lack adequate power to reliably explore these associations. Similarly, for studies of cancer mortality, positive associations have been shown for cancers of the pancreas, liver, colon and rectum, and bladder (5). However there is little data for mortality of rare cancer outcomes.

For type 1 diabetes, evidence is limited and variable. Cohort studies have shown a 10–37% increased risk for the incidence of all cancers combined, whereas case-control studies showed no association (6). Studies are rarely large enough to explore site-specific cancer incidence. However, there is evidence to suggest an increased risk for cancers of the pancreas, liver, and stomach (6). The evidence of cancer-specific mortality among type 1 diabetic cohorts is even more limited.

Hyperglycemia, insulin resistance, hyperinsulinemia, and the effects of treatment for diabetes have all been suggested as possible mechanisms for cancer risk (7). Since insulin resistance and hyperinsulinemia are much more prominent in type 2 than type 1 diabetes, although hyperglycemia is more similar between the two, investigating both diabetes types may shed light on the likely mechanistic pathway. It has also been argued that the observed associations could be due to biases not adequately addressed by the majority of previous studies. Reverse causality is possible, particularly for pancreatic cancer, whereby dysfunction in insulin secretion as a consequence of tumor growth may be sufficient to induce hyperglycemia (2). Detection bias might also exist due to increased disease surveillance among diabetic patients, particularly in the period shortly after diabetes diagnosis (8). Finally, nonspecific systemic symptoms from a cancer may lead to earlier detection of diabetes, which also contributes to a relative overrepresentation of people with undiagnosed cancers among newly diagnosed diabetic patients.

We use an Australian diabetes registry to investigate associations of diabetes and cancer. We also explore whether these estimates are impacted by reverse causation and detection bias.

**RESEARCH DESIGN AND METHODS**

**Data Sources**
The National Diabetes Service Scheme (NDSS) is an Australian Government initiative established in 1987 to deliver diabetes-related products at subsidized prices and provide information to people with diabetes. Registration of patients is free and is completed by a medical practitioner or credentialed diabetes nurse educator. The NDSS captures 80–90% of all Australians with known diabetes (9).

We included all individuals with type 1 or type 2 diabetes who were on the NDSS between 1 January 1997 and 31 December 2008. The year 1997 was chosen as the start date, as this time followed a unification of state-based registries as well as an improvement in data quality. Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were classified as type 1 on the NDSS and were diagnosed before the age of 30 years, and the time between diagnosis date and date of first insulin use was <1 year. For those missing data on date of diagnosis (59.1% type 1 diabetes and 36.1% type 2 diabetes) or insulin initiation date (many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years), we classified people as type 1 if they were recorded as type 1 on the registry, were taking insulin, and were registered at ≤45 years of age. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1 (10). All others were classified as type 2 diabetic.

The Australian Cancer Database (ACD) is a register of all primary, malignant cancers diagnosed in Australia since 1982. It is a statutory requirement to notify the registry of all cases of malignant neoplasms. Only the first occurrence of a site-specific cancer is recorded; recurrences and metastases are not. All recorded cancers were coded according to the ICD-10.

**Data Linkage**
The NDSS was linked to the National Death Index (NDI) and the ACD, using data up to and including 31 December 2008. NDI and ACD data beyond this date were not available at the time of linkage. Linkage was performed by the Australian Institute of Health and Welfare (AIHW) using first name, second name, last name, sex, and date of birth (11). The record linkage methodology assigns each compared pair of records a record pair comparison weight. Based on clerical review of a sample of these links, it is expected that links with a weighting of low, medium, and high correspond to a link accuracy (positive predictive value) of 96.75, 98.97, and 99.90%, respectively. For this study, we chose a medium cutoff point with a predictive value of 98.97% as this has shown to be a reliable cutoff in other, similar studies (12).

**Statistical Analysis**
Individuals were followed from 1 January 1997, or registration date if thereafter, to 31 December 2008, date of death, and date of event (death or cancer occurrence). Incidence of cancer was defined as the first occurrence of cancer, or death from cancer if that was the first time the cancer had been reported. For “overall cancer incidence,” only the first reported cancer was included. Anyone with a previous nonfatal cancer diagnosis between 1982 and either 1997 or date of NDSS registration (whichever was the later) was excluded (n = 33,621). Observed cancer incidence and mortality rates by single calendar year, 5-year age-group, and sex were calculated among people with diabetes, to match the format of the available cancer incidence and mortality rates in the general population. Given that deaths at older ages can be difficult to
attribute to a single cause, we only analyzed follow-up until age 75 years.

Cancer incidence and mortality in the diabetic population was compared with the general Australian population using standardised incidence ratio (SIR) and mortality ratio (SMR), stratified by sex. The SIR/SMRs were computed by fitting a Poisson model for the number of events using the log of the expected number of events as offset. The expected number of events was computed using published cancer incidence and mortality rates as provided by AIHW. SIR/SMR estimates for breast cancer were calculated for total breast cancer and then stratified by pre- and postmenopausal status using age 50 years as a proxy for menopausal status.

To explore the possibility of detection bias and reverse causality, we split the follow-up time (for both incidence and mortality) into different time periods following NDSS registration date, at 3, 6, 12, and 24 months, and estimated separate rate ratios for each of the intervals. Time since NDSS registration was subdivided into intervals that were short shortly after diagnosis and longer later. This was motivated by other studies (8,13) that have shown a substantial variation in the hazard ratio by time since diabetes diagnosis, particularly shortly after diagnosis. This analysis was done among the total type 2 diabetic population (to increase power) and for cancers with an adequate number of outcomes. The number of cancer outcomes among type 1 diabetes was too low to split by follow-up time.

All analyses were done using STATA version 12.1 (Statacorp, College Station, TX). This study was approved by the Alfred Health Human Ethics Committee and the AIHW Ethics Committee.

**RESULTS**

This study included 953,382 NDSS registrants, 80,676 (8.5%) with type 1 diabetes and 872,706 (91.5%) with type 2 diabetes, whose baseline characteristics and total cancer outcomes are described in Table 1.

Table 1—Descriptive characteristics of the NDSS population, 1997–2008

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>80,676</td>
<td>872,706</td>
</tr>
<tr>
<td>Males (%)</td>
<td>52.1</td>
<td>53.2</td>
</tr>
<tr>
<td>Median follow-up time (years)</td>
<td>12.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Insulin use (%)</td>
<td>100</td>
<td>32.4</td>
</tr>
<tr>
<td>Age at diagnosis*</td>
<td>21.6 (11.6, 32.4)</td>
<td>59.5 (50.2, 69.2)</td>
</tr>
<tr>
<td>Age at registration*</td>
<td>27.4 (15.1, 36.6)</td>
<td>60.4 (51.1, 69.7)</td>
</tr>
<tr>
<td>Cancer (n)</td>
<td>2,079</td>
<td>70,406</td>
</tr>
<tr>
<td>Cancer deaths (n)</td>
<td>593</td>
<td>26,333</td>
</tr>
</tbody>
</table>

*Median (25th, 75th percentiles).

For type 1 diabetes, no significant SIRs were seen for all breast cancers combined, or premenopausal breast cancer (data not shown). For type 2 diabetes, significant SIRs were seen for all breast cancers combined (data not shown) and postmenopausal breast cancer, but not premenopausal cancer. As the majority of breast cancer cases occurred after menopause, all subsequent results refer only to postmenopausal breast cancer.

For type 1 diabetes, no significant SIRs were observed for cancers of the pancreas, liver, esophagus, colon and rectum, stomach, thyroid, brain, lung, ovarian, and endometrium, and a decreased risk for melanoma. The SIRs in males were generally increased for the same cancers, but fewer were significant, and a decreased risk for prostate cancer was also observed. For type 2 diabetes, SIRs for all cancers combined were 1.08 (1.07–1.09) and 1.22 (1.20–1.23) among males and females, respectively (Fig. 18). Significant SIRs were observed for all cancers, excluding brain, anal (females), and testicular cancers, and esophageal cancer (females). Significant decreased risks were also observed for melanoma and prostate cancers. The highest excess risks were observed for cancers of the liver and pancreas. SIR values for type 1 and type 2 diabetes are detailed in Supplementary Tables 1 and 3 (for total population).

For type 1 diabetes, no significant SIRs were observed for cancers of the pancreas, liver, and kidney and Hodgkin’s lymphoma. Significant SIRs were also observed for cancers of the pancreas, liver, and kidney and Hodgkin’s lymphoma. Significant SIRs were also observed for stomach, gallbladder, and non-Hodgkin’s lymphoma among females only. SMR estimates are detailed in Supplementary Tables 2 and 3 (total population).

To explore the contribution of reverse causation and detection bias, we calculated SIRs and SMRs in type 2 diabetes over time. For SIRs, there was a clear elevation in risk for all cancer, and each site-specific cancer within the first 3 months of NDSS registration (Fig. 3A and Supplementary Table 4). Over time, excess risks reduced but remained significantly higher than the general population for all cancer, pancreas, liver, colon and rectum, kidney, bladder, non-Hodgkin’s lymphoma, thyroid, breast, and endometrial cancers. Additionally, SIRs for prostate cancer were elevated in the first 3 months, but this became a significantly decreased risk from 12–24 months after NDSS registration.

For SMRs, there were no differences in estimates across different time periods following NDSS registration for all cancer, non-Hodgkin’s lymphoma, and prostate and breast cancers (Fig. 3B and Supplementary Table 5). For kidney, colon and rectum, bladder, and lung cancers, point estimates in the early time periods following NDSS registration were protective. As time after NDSS registration increased, SMR estimates approached the null, and for kidney cancer were significantly elevated. For liver cancer, there was no increased risk of mortality within 3 months of NDSS registration, but there was a stable, elevated SMR from 3 months onwards. Last, for thyroid and pancreatic
cancers, early SMR estimates were high, and these became lower as time progressed but remained elevated relative to the general population.

Separate sensitivity analyses using NDI cutoffs with linkage rates of 99.9 and 96.75%, and using a cutoff date of age <40 years at registration for classification as type 1 diabetes among those missing data on age at diagnosis, did not change the overall pattern of results (data not shown).

CONCLUSIONS
In this study, we found excess risks of incidence and mortality for a number of cancers among both type 1 and type 2 diabetes, with the highest excess risks observed for pancreas, liver, and...
endometrium, kidney, thyroid, chronic myeloid leukemia, and gallbladder cancers. Detection bias and/or reverse causation appear to explain some, but not all, of this excess risk, which often remains beyond 2 years after NDSS registration date.

Comparison With the Literature
Risk estimates for type 1 and type 2 diabetes in this study are lower compared with findings from other studies. A registry-based study in Denmark reported incident rate ratios for overall cancer of 1.2 and 1.4 for noninsulin and insulin users, respectively (13). Significant associations were also observed in that study for liver, pancreas, stomach, kidney, colon and rectum, endometrium, and lymphoma cancers, with rate ratios in the insulin group generally higher than the noninsulin group. Our lower estimates relative to this study may be attributed to the use of national population rates as the comparator (rather than a nondiabetic population). SIR estimates for type 2 diabetes obtained in our study are also comparable to previous meta-analyses performed on site-specific cancer incidence (4,14–20). We add to the current literature around type 2 diabetes and cancer incidence more precise risk estimates for some of the less common cancers. Our finding of a reduced risk of prostate cancer in type 1 diabetes suggests that factors other than obesity-induced low testosterone levels are responsible for the observation.

For cancer mortality outcomes in type 2 diabetes, estimates for all cancer, pancreas, liver, and bladder are similar to previous studies (21–24). We additionally show significant excess risks for mortality from cancers of the kidney, stomach, gallbladder, and endometrium, non-Hodgkin’s lymphoma, and Hodgkin’s lymphoma, which have previously not been shown. This study is one of the first studies to explore site-specific cancer mortality in type 1 diabetes. Estimates of risk were similar to those for type 2 diabetes, but fewer individual cancer types were significant. The lack of significant findings for type 1 diabetes and site-specific cancer mortality highlights the difficulty in assessing these relationships given the rarity of both of these conditions, the potentially long time lag between diabetes diagnosis and cancer death, and thus the need for extremely large cohort studies to explore these associations. Additionally, it should be noted that this is one of the first analyses of diabetes and cancer mortality whereby incident cancers were excluded prior to NDSS registration. Excluding prior incident cancers helps to disentangle the temporal association between diabetes and cancer incidence (and subsequent mortality).

Few studies to date have addressed the temporal relations between diabetes and cancer risk. A study by Johnson et al. (8) in Canada found a substantial degree of detection bias in the diabetic population, with elevated rate ratios reported in the first 3 months after diabetes diagnosis for all site-specific cancers, as did a Danish study (13). We also observed an initial elevated excess risk of cancer incidence at the time of NDSS registration, which fell over time but remained significantly elevated beyond 2 years for all but lung and prostate cancer. Even prostate cancer, for which diabetes is protective, had an increased SIR in the first 3 months. The SIRs clearly point toward increased cancer screening within the first few months of diabetes diagnosis due to increased medical attention, subsequently leading to earlier detection of any present and previously undiagnosed cancer, but also show the persistence of the relationship over time.

We noted three patterns of risk when modeling SMRs over time. The first, for bladder, lung, and colorectal cancers,
showed a protective SMR in the first few months after NDSS registration, which then became null over time. The low mortality risk in the first 3 months suggests that diabetes diagnosis improves short-term cancer survival or that people with advanced cancer are less likely to appear on the NDSS. The latter is much more likely and could be due to weight loss reducing diabetes incidence or to a reluctance to diagnose diabetes or register a patient on the NDSS if the cancer is very advanced. The second pattern, observed for kidney, breast, endometrium, and non-Hodgkin’s lymphoma, showed no difference in SMR estimates over time. Persisting elevation of SIR, but without an accompanying increase in SMR, suggests increased screening (detection bias) in people with diabetes. The failure of screening to translate into reduced mortality could be due to a lack of benefit of screening or to an offset of the benefits of screening by poorer responses to therapy (25) or by a real increase in incidence. Third, for pancreas, thyroid, and liver cancers, SMRs fell over time but remained elevated beyond 2 years for liver and pancreatic cancer, suggesting reverse causality only explains some of the relationship and that type 2 diabetes is a genuine risk factor for these two cancers. The varying relationships between SIR and SMR across cancers over time indicate a complex interplay of real effects of diabetes on cancer, detection bias, reverse causality, and cancer treatment factors.

Last, we show that the magnitudes of excess risk for type 1 and type 2 diabetes are generally similar, with overlapping 95% CIs; albeit fewer outcomes are significant for type 1 diabetes, most likely due to limited power. Given the different etiologies of these diseases with respect to insulin availability, if hyperinsulinemia was the driving force between diabetes and cancer, we would expect our results to be moderated by diabetes type. Our results, instead, support the concept that hyperglycemia, found in both type 1 and type 2 diabetes, may be the mechanistic driver between diabetes and cancer. Hyperglycemia can induce DNA damage (26), downregulate expression of antioxidants (27), and increase reactive oxygen species generation (28). Although biologically plausible, results from epidemiological studies are conflicting. The “hyperglycemia hypothesis” is supported by large inception cohort studies that demonstrate a strong relationship between elevated blood glucose and cancer incidence or mortality (24, 29–31). However, a recent meta-analysis reported a nonsignificant pooled risk ratio for cancer incidence of 0.91 (95% CI 0.79–1.05) for subjects with improved glycemic control across three trials, compared with those in the control arms of the studies, suggesting that improved glycemic control does not confer a reduced risk of cancer among diabetic patients (32). Several other key mechanisms linking diabetes and cancer include poor diet, physical inactivity (33), genetic predisposition (34), and possibly some diabetes treatments, such as insulin (35). Information on these possibly modifying factors is not available for the entire population, and since this is a population-based study, the influence of these factors could not be explored further.

Strengths and Limitations

The main strength of this study is that it is population based with a large sample size, long follow-up time, and the ability to distinguish between type 1 and type 2 diabetes. There are several limitations, however, that should be acknowledged. First, the NDSS is an administrative database and hence lacks precise information about type of diabetes for all registrants. The classification of diabetes is challenging and misclassification can occur. However, the proportions of type 1 and type 2 diabetes in this study (8.5 vs. 91.5%) are similar to other Australian data (36). Further, the proportion of type 2 diabetes who were also on insulin is consistent with other studies (37). Second, the NDSS does not include undiagnosed diabetes, and the NDSS may underrepresent diet-controlled diabetes as the diabetes-related products provided through the scheme may not be needed. Third, the large sample size in this study enabled us to stratify results by sex, numerous cancer sites, and multiple time periods. By conducting multiple analyses on the same dataset, we have of course increased the possibility of chance findings if we were only using P values as guiding principle. Last, in a population-wide study, it is not possible to explore the extent to which obesity, smoking, socioeconomic position, family history of cancer, and/or pharmaceutical treatments contributed to the observed association between diabetes and cancer. However, studies based on cohorts with detailed information on type 2 diabetes that were able to account for obesity, lifestyle-related factors, and diabetes treatment have still observed elevated risks for a number of cancers (38, 39). Therefore, it is unlikely that these factors explain the entire association between diabetes and cancer.

Using one of the largest diabetes registries in the world, we show that both type 1 and type 2 diabetes are associated with an excess risk of incidence and mortality for overall and a number of site-specific cancers. Detection bias and reverse causality may partly explain the stark increase in risk of cancer immediately following diabetes diagnosis, but they do not explain increased risks >2 years following diabetes diagnosis, particularly for cancers of the pancreas, liver, kidney, and endometrium. We suggest future analyses on type 2 diabetes and cancer should account for the presence of detection bias and reverse causation, particularly in the first 3 months post–diabetes diagnosis. Screening for cancers, according to standard protocols for the general population, in diabetic patients should be emphasized in clinical practice, as early detection is key to preventing premature mortality.

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References