Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People

Suping Ling,[1] Karen Brown,[2] Joanne K. Miksza,[1] Lynne Howells,[2] Amy Morrison,[1] Eyad Issa,[2,3] Thomas Yates,[1,4] Kamlesh Khunti,[1] Melanie J. Davies,[1,4] and Francesco Zaccardi[1]

Diabetes Care 2020;43:2313–2322 | https://doi.org/10.2337/dc20-0204

BACKGROUND AND PURPOSE

Whether the association between type 2 diabetes (T2D) and cancer is causal remains controversial. The goal of this work is to assess the robustness of the observational associations between T2D and cancer to unmeasured confounding.

DATA SOURCES AND STUDY SELECTION

PubMed, Web of Science, and the Cochrane library were systematically searched on 10 January 2019 for observational studies investigating associations between T2D and cancer incidence or mortality.

DATA EXTRACTION AND DATA SYNTHESIS

Cohort-level relative risk (RR) was extracted. RRs were combined in random-effects meta-analyses and pooled estimates used in bias analyses. A total of 151 cohorts (over 32 million people, 1.1 million cancer cases, and 150,000 cancer deaths) were included. In meta-analyses, T2D was associated with incidence of several cancers, from prostate (RR 0.83; 95% CI 0.79, 0.88) to liver (2.23; 1.99, 2.49), and with mortality from pancreatic cancer (1.67; 1.30, 2.14). In bias analyses, assuming an unmeasured confounding associated with both T2D and cancer with a RR of 1.5, the proportion of studies with a true effect size larger than a RR of 1.1 (i.e., 10% increased risk in individuals with T2D) was nearly 100% for liver, pancreatic, and endometrial, 86% for gallbladder, 67% for kidney, 64% for colon, 62% for colorectal, and <50% for other cancer incidences, and 92% for pancreatic cancer mortality.

LIMITATIONS

Biases other than unmeasured confounding were not analytically assessed.

CONCLUSIONS

Our findings strongly suggest a causal association between T2D and liver, pancreatic, and endometrial cancer incidence, and pancreatic cancer mortality. Conversely, associations with other cancers were less robust to unmeasured confounding.

[1]*Leicester Diabetes Research Centre, College of Life Sciences, University of Leicester, Leicester, U.K.*
[2]*Leicester Cancer Research Centre, Leicester Royal Infirmary, University of Leicester, Leicester, U.K.*
[3]*Leicester HPB Unit, Leicester General Hospital, Leicester, U.K.*
[4]*National Institute for Health Research (NIHR) Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust and the University of Leicester, Leicester, U.K.*

Corresponding author: Suping Ling, sl617@leicester.ac.uk

Received 28 January 2020 and accepted 28 May 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12430328.

© 2020 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/content/license.

Downloaded from http://ada.silverchair.com/c... 24

META-ANALYSIS

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia, resulting from deficient insulin secretion and/or action (1). It was estimated that 425 million people worldwide were affected by diabetes in 2017, with more than 90% being patients with type 2 diabetes (T2D) (2). Compared with their counterparts, people with T2D have a higher risk of premature death, mainly attributable to cardiovascular diseases (3).

In original longitudinal studies and meta-analyses, diabetes has also been associated with an increased risk of cancer incidence and mortality (4,5). However, it remains unclear whether T2D is causally related to cancer or rather the association is confounded by other factors connected to both T2D and cancer. In fact, the increasing prevalence and earlier onset of T2D coincides with that of overweight and obesity (6,7). Therefore, it has been argued that the association between T2D and cancer could be noncausal and rather reflect a true, causal link between excess adiposity and cancer. Delineating the causality between T2D and specific cancers is important for identifying high-risk groups that could be efficiently targeted for early detection strategies and preventive interventions. Detecting and treating cancers at an earlier stage will lead to improved patient outcomes and survival (8).

In an experimental setting, confounding may be controlled for by randomization. This process, however, is not always feasible. Adjustment for confounders is, therefore, one of the most common approaches to control for confounding in observational studies. Residual confounding from unmeasured factors may still exist and bias the estimation. Such bias may be quantified in a sensitivity analysis (also known as bias analysis). This analysis enables researchers to quantify the sensitivity of associations to unmeasured confounders, i.e., the strength to which the unmeasured confounder(s) need to be associated to the exposure (T2D) and outcome (cancer) to nullify the association. This analytical strategy therefore helps estimate the likelihood of causality between an exposure and an outcome, both in the original observational studies and the meta-analysis (9,10). It has been used in previous studies on hypoglycemia and cardiovascular diseases (11), nonalcoholic fatty liver disease and T2D (12), or physical activity and liver cancer (13), but not in the context of T2D and cancer.

In this study, we conducted a systematic review and meta-analysis with bias analysis for unmeasured confounding to quantify the proportion of studies with an unconfounded association between T2D and risk of cancer incidence and mortality, thereby helping to characterize the nature of this relationship.

METHODS

Data Sources and Searches

We updated the search of the umbrella review on T2D and cancer published in 2015, which included all relevant meta-analyses up to December 2013 (4). On 10 January 2019, we searched PubMed, Web of Science, and the Cochrane Library of Systematic Reviews for meta-analyses and original observational studies that reported on the association between diabetes and cancer incidence or mortality. The search keywords and algorithm are presented in Supplementary Fig. 1. We screened titles, abstracts, and bibliographies of all relevant meta-analyses. Articles were included for further review if it was uncertain whether to exclude them at this stage. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting this meta-analysis (14). The PRISMA checklist is shown in the Supplementary Material.

Study Selection

Studies were eligible if they reported the estimates (with 95% CIs, SEs, or *P* values) for the longitudinal association of T2D with cancer incidence or mortality. Following the rare disease assumption (low number of cancer events), we assumed rate ratio, hazard ratio, and odds ratio to approximate the relative risk (RR) (15). Studies were excluded if *1*) the reported association was based on the comparison between people with diabetes and the general population (instead of people without diabetes); *2*) the cohort focused on some specific populations (e.g., patients with infections associated with a higher risk of cancer) or explicitly included type 1 diabetes only; *3*) the exposure-outcome association was reported for continuous change of glucose levels; *4*) the outcome was not cancer incidence or mortality (e.g., adenoma); *5*) several cohorts were combined and the estimate for each cohort was not available. If articles used the same database with no overlapping populations and calendar years of follow-up, we included them as distinct cohorts. If several articles reported the same outcome and used the same cohort, we included that with the largest person-time-at-risk value.

Data Extraction and Quality Assessment

We used a standardized form to extract data on age, follow-up duration, BMI, exposures, outcomes, and confounders for each included cohort, as well as number of events and participants, person-years and the most-adjusted estimates for each outcome. We assessed the quality of studies using the Newcastle-Ottawa Scale (NOS) (16), in which we considered age, sex, and BMI as key confounders in the association between T2D and cancer.

Data Synthesis and Analysis

A within-cohort fixed-effect meta-analysis was firstly performed to obtain an overall estimate if RRs were stratified (e.g., by sex or age groups). Our primary analyses sought to quantitatively pool the RR of associations between T2D and each cancer incidence or mortality in both sexes and detect any potential bias from unmeasured confounding. To include the largest set of individuals, we also included cohorts that only reported on one sex in our primary analyses. Meta-analyses and bias analyses were also stratified by sex, where possible.

For each outcome, RRs were meta-analyzed using a restricted maximum-likelihood random-effects model with CIs obtained by the Knapp and Hartung method (17). Heterogeneity across cohorts was quantified by I^2 statistics (18), and publication bias was assessed with the funnel plot and Egger's test (19). The bias analysis for unmeasured confounding in a meta-analysis, following the methodology proposed by Mathur and VanderWeele (9), quantifies the proportion of studies with a scientifically meaningful effect size (i.e., if it is assumed an increased risk in individuals with T2D, a true effect size above a prespecified RR; otherwise, below a prespecified RR) for various magnitudes of unmeasured confounding. Considering a certain amount of unmeasured confounding, the larger the proportion of studies with the true effect size, the more likely the association is causal. The stronger the unmeasured

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

Table 1—Cohort-level information for each cancer outcome

Cancer	Males only (*n*/*N*)	Females only (*n*/*N*)	Median of mean age (years) across cohorts			Median of mean follow-up (years) across cohorts			Median of mean BMI (kg/m^2) across cohorts			Confounding adjustment: *n* (%) of cohorts adjusted for					
			No.	DM	NDM	No.	DM	NDM	No.	DM	NDM	Age	Sex	BMI	Smoking	Alcohol	Others
Incidence																	
All-site	1/30	0/30	23	62	56	14	9	10	6	25	25	29 (96.6)	29 (96.6)	14 (46.6)	15 (50.0)	11 (36.6)	24 (80.0)
Bladder	2/30	2/30	24	62	58	16	9	9	3	23	23	28 (93.3)	29 (96.6)	13 (43.3)	13 (43.3)	10 (33.3)	24 (80.0)
Breast	0/32	32/32	25	62	58	15	8	9	6	27	25	31 (96.9)	31 (96.8)	17 (53.1)	13 (40.6)	12 (37.5)	26 (81.2)
Colon	2/24	2/24	19	64	62	13	11	11	5	26	27	24 (100)	24 (100)	16 (66.6)	11 (45.8)	10 (41.6)	21 (87.5)
Colorectal	5/47	4/47	37	62	58	23	10	11	11	28	25	46 (97.9)	46 (97.8)	24 (51.0)	24 (51.0)	18 (38.2)	39 (82.9)
Endometrium	0/15	15/15	13	62	61	11	7	9	3	28	25	14 (93.3)	14 (93.3)	7 (46.6)	2 (13.3)	3 (20.0)	13 (86.6)
Esophagus	1/19	1/19	17	62	62	6	10	11	3	23	23	19 (100)	19 (100)	8 (42.1)	7 (36.8)	7 (36.8)	17 (89.4)
Gallbladder	1/17	1/17	15	61	52	7	11	11	4	23	23	17 (100)	17 (100)	10 (58.8)	10 (58.8)	8 (47.0)	13 (76.4)
Kidney	2/23	2/23	19	63	59	9	8	9	4	26	25	23 (100)	23 (100)	11 (47.8)	11 (47.8)	9 (39.1)	19 (82.6)
Leukemia	1/12	0/12	10	63	60	4	11	11	1	23	23	12 (100)	12 (100)	5 (41.6)	5 (41.6)	4 (33.3)	10 (83.3)
Liver	3/36	3/36	29	61	55	17	11	12	8	24	23	32 (88.9)	33 (91.6)	18 (50.0)	18 (50.0)	16 (44.4)	29 (80.5)
Lung	2/32	2/32	26	61	56	17	8	8	7	26	24	31 (96.9)	31 (96.8)	17 (53.1)	17 (53.1)	14 (43.7)	26 (81.2)
Melanoma	1/11	0/11	9	61	60	4	7	10	0	—	—	11 (100)	11 (100)	3 (27.2)	1 (9.1)	1 (9.1)	9 (81.8)
NHL	1/19	0/19	14	63	52	9	8	9	0	—	—	19 (100)	19 (100)	8 (42.1)	6 (31.5)	4 (21.0)	14 (73.6)
Ovary	0/20	20/20	17	64	60	9	8	9	2	25	24	19 (95.0)	19 (95.0)	9 (45.0)	6 (30.0)	5 (25.0)	17 (85.0)
Pancreas	3/38	3/38	31	62	58	15	10	10	9	26	26	36 (94.6)	36 (94.7)	17 (44.7)	19 (50.0)	14 (36.8)	31 (81.5)
Prostate	39/39	0/39	27	62	59	18	9	9	9	26	25	35 (89.6)	38 (97.4)	18 (46.1)	17 (43.5)	10 (25.6)	33 (84.6)
Rectum	2/24	2/24	19	64	62	13	11	11	5	26	27	24 (100)	24 (100)	16 (66.6)	11 (45.8)	10 (41.6)	21 (87.5)
Stomach	2/28	2/28	24	62	56	14	8	8	5	25	24	28 (100)	28 (100)	14 (50.0)	13 (46.4)	11 (39.2)	23 (82.1)
Thyroid	1/14	0/14	12	62	58	8	9	10	2	31	27	13 (92.9)	13 (92.8)	5 (35.7)	4 (28.5)	2 (14.2)	12 (85.7)
Mortality																	
All-site	2/17	1/17	11	59	55	9	16	16	9	27	26	17 (100)	16 (94.1)	13 (76.4)	16 (94.1)	9 (52.9)	14 (82.3)
Pancreas	1/11	0/11	8	56	51	6	17	17	5	26	25	11 (100)	11 (100)	6 (54.5)	10 (90.9)	5 (45.4)	8 (72.7)

Dash indicates not available. DM, people with diabetes; Females only (n/N), number of cohorts including only females; Males only (n/N), number of cohorts including only males; NDM, people without diabetes; No., number of cohorts reporting relevant information.

confounding needed to be to reduce the proportion of studies with the true effect size, the more likely the association is causal. If no unmeasured confounding was needed to reduce the proportion (i.e., unmeasured confound with a RR of 1.0), the association is considered unlikely to be causal. In the current analysis, we modeled a wide range of possibilities: we estimated the proportion of studies with a true effect size stronger than various prespecified RRs, ranging from 0.5 to 2.0 (20), assuming the unmeasured confounding factor associated with both T2D and cancer with various RRs, ranging from 1.0 to 4.0 (Supplementary Fig. 2). In line with Mathur and VanderWeele (9), we selected a prespecified RR of 1.1 and 0.9 (i.e., 10% increased or decreased risk, respectively) as the minimum threshold for an apparently causative association. We considered the association between T2D and cancer likely to be causal if the proportion of studies with the effect size stronger than this minimum threshold was more than 70% (9), accounting for an unmeasured confounding with a RR of 1.5 based on the levels of adjustments in the individual studies included in the meta-analysis (Table 1). With constant prespecified RR and unmeasured confounding RR, a greater proportion suggests a stronger evidence for a causal relationship. Estimates for other combinations of confounding strengths, prespecified RRs, and proportions were also calculated, and they are available on GitHub (21) for main and sex-stratified analysis. To compare the probabilities of causality among different cancers, bias analyses were conducted for cancer-specific outcomes reported in at least 10 cohorts. As the current bias analysis specifically evaluates the robustness to unmeasured confounding, to minimize other sources of bias, such as reverse causality and detection bias, we have further conducted analyses including only studies where such biases were deemed low (i.e., studies with appropriate outcome assessment and long enough and adequate follow-up, using the criteria reported in the outcome section in the NOS) (16).

All analyses were conducted in R for Windows (version 3.6.1) using the "Evalue" and "metafor" packages (10,22); Stata/IC 16.0 (StataCorp, College Station, TX) was used for data manipulations and graphs. Two-side P value <0.05 was nominally considered statistically significant; results are reported with 95% CIs.

RESULTS

Characteristics of Included Studies

We identified 2,138 reports in the systematic search. After title and abstract screening and manual review of bibliographies of 45 meta-analyses, 351 articles were deemed relevant for full-text assessment (Supplementary Fig. 1). Of them, 154 articles, including 163 cohorts, reported estimates on the association between T2D and cancer incidence or mortality. The studies excluded and reasons for exclusion are reported in Supplementary Table 1. We analyzed outcomes if they were reported in 10 or more cohorts. As a result, 144 articles with 151 cohorts were included in the final quantitative analysis, with information on over 32 million people, 1.1 million incident cancer cases, and 150,000 cancer deaths. References of the included studies are reported in the Supplementary Material.

The characteristics of the included cohorts are presented in Supplementary Table 2. The quality of studies was medium to high: the NOS score ranged from 4 to 9 (out of 9) with a median of 7 (Supplementary Fig. 3). Of the 151 included cohorts, 128 reported RRs only on cancer incidence, 18 only on cancer mortality, and 5 on both. Overall, the quantitative analyses were possible for all-site cancer incidence and mortality, 19 cancer-specific sites for incidence, and only pancreatic cancer for mortality. The number of cohorts ranged from 47 for colorectal cancer incidence to 11 for melanoma and pancreatic cancer mortality. Stratified analyses by sex were possible for all-site cancer incidence and mortality and for an additional 10 for cancer-specific incidence. Table 1 shows the cohort-level information for each cancer outcome.

Meta-analyses

Thirty cohorts, including 15,498,790 individuals and 816,630 incident cancer cases, reported on the association between T2D and all-site cancer incidence. The pooled RR was 1.15 (95% CI 1.10, 1.21), with heterogeneity across cohorts (I^2 = 98.8%, $P < 0.001$) (Fig. 1). The cohort-specific RRs ranged from 0.93 (0.93, 0.93) to 1.80 (1.27, 2.55) (Supplementary Fig. 4*A*). For cancer-specific incidence, meta-analyses showed that T2D was associated with a decreased risk of prostate cancer (pooled RR: 0.83; 0.79, 0.88) but an increased risk of female breast (1.10; 1.05, 1.15), non-Hodgkin lymphoma (1.12; 1.02, 1.24), ovary (1.14; 1.03, 1.26), bladder (1.19; 1.09, 1.29), leukemia (1.19; 1.07, 1.31), stomach (1.19; 1.05, 1.35), thyroid (1.20; 1.12, 1.29), rectum (1.23; 1.13, 1.35), colorectal (1.29; 1.23, 1.36), colon (1.30; 1.22, 1.39), kidney (1.32; 1.21, 1.44), gallbladder (1.61; 1.34, 1.93), endometrium (1.63; 1.41, 1.88), pancreas (2.09; 1.88, 2.33), and liver (2.23; 1.99, 2.49) cancers, with significant heterogeneity across cohorts in all analyses (I^2 ranging from 51.3% for ovarian to 94.8% for liver cancer) except thyroid cancer (I^2 = 28.3%) (Fig. 1 and Supplementary Fig. 4*A–C*). Meta-analyses did not show significant associations between T2D and incidence of esophageal cancer (1.01; 0.89, 1.15), lung (1.05; 0.99, 1.12), or melanoma (1.06; 0.95, 1.19) (Fig. 1).

Seventeen cohorts, including 3,500,363 people and 147,480 cancer deaths, reported on the association between T2D and all-site cancer mortality. The pooled RR was 1.25 (95% CI 1.18, 1.33), with heterogeneity across cohorts (I^2 = 80.4%, $P < 0.001$) (Fig. 1). The cohort-level RRs ranged from 0.74 (0.45, 1.21) to 1.57 (1.12, 2.20) (Supplementary Fig. 4*C*). Cancer-specific mortality was only available for pancreatic cancer (1.67; 1.30, 2.14), with heterogeneity across cohorts (I^2 = 65.3%, P = 0.002) (Supplementary Fig. 4*C*).

Funnel plots for all outcomes are presented in Supplementary Fig. 5*A* and *B*. There was no clear evidence of publication bias.

In sex-stratified analyses, the pooled associations between T2D and all-site cancer incidence and mortality were slightly higher in females than males (Fig. 1): 1.20 (95% CI, 1.11, 1.29) vs. 1.11 (1.04, 1.19) for incidence and 1.28 (1.18, 1.40) vs. 1.21 (1.13, 1.30) for mortality. A slightly higher heterogeneity for all-site cancer incidence versus mortality was also observed: 89.8% vs. 77.0% in females and 97.1% vs. 74.6% in males. Figure 1 shows sex-stratified pooled estimates for cancer-specific incidence. Supplementary Fig. 6*A–C* gives the cohort-level estimates, and Supplementary Fig. 7*A* and *B* provides the corresponding funnel plots.

Supplementary Tables 3 and 4 report results of the meta-analyses restricted

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

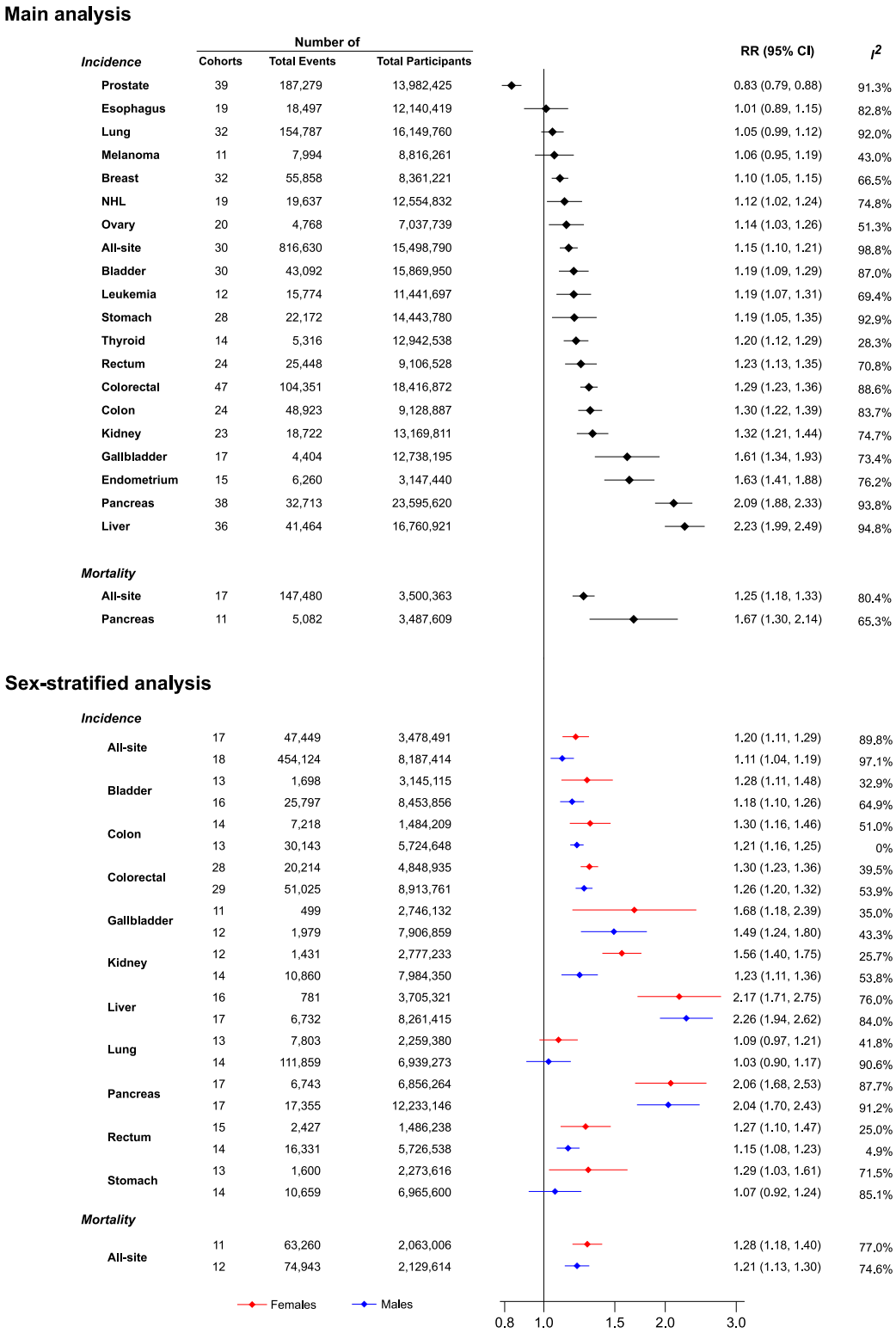

Figure 1—Meta-analyses of all-site and site-specific cancer incidence and mortality. RR, pooled relative risk.

to 120 cohorts with adequate outcome assessment and follow-up. The pooled RRs and heterogeneity for each outcome were generally consistent with those quantified in the main analysis.

Bias Analyses

There were 19 cancer-specific incidence and 1 mortality outcomes available for bias analyses. Figure 2 shows the proportions of studies with the true effect size stronger than various prespecified RRs, ranging from 0.5 to 1.0 for prostate cancer incidence and from 1.0 to 2.0 for all other cancer outcomes, under an unmeasured confounding strength ranging from 1.0 to 4.0. Sex-stratified estimates are shown in Supplementary Fig. 8.

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

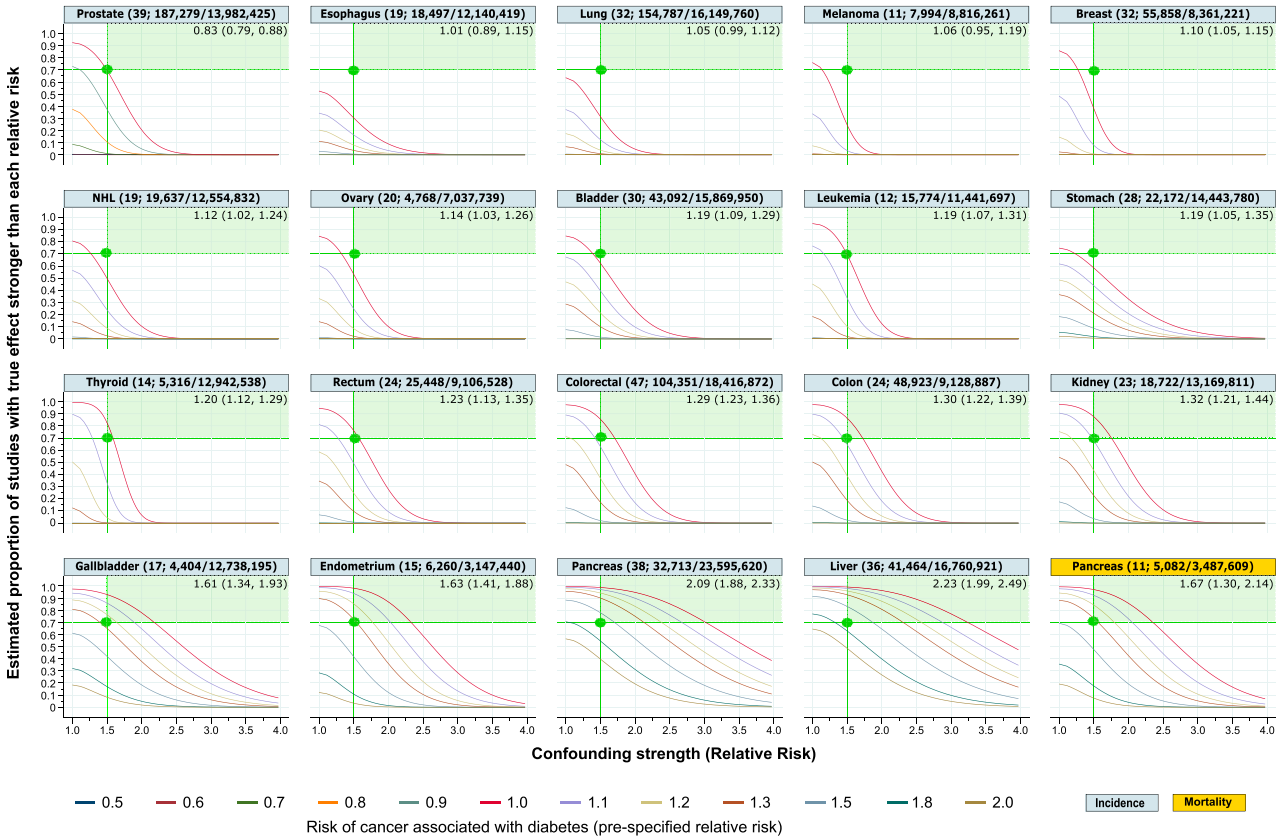

Figure 2—Proportions of studies with a true effect stronger than various prespecified RRs. Subtitles show the cancer-specific number of cohorts and number of events/people. Within each panel is shown the pooled RR with 95% CI derived from the random-effects meta-analysis. X-axes show the unmeasured confounding strength, associated with both diabetes and cancer, with a RR ranging from 1.0 to 4.0 (green grid line: 1.5). Y-axes show the proportions of studies with the true effect stronger than each prespecified RR for the association between diabetes and cancer: 0.5 to 1.0 for prostate cancer incidence and 1.0 to 2.0 for other outcomes (green grid line: 70%). The lines show each prespecified RR. The green areas show whether the association between T2D and cancer is likely to be causal if the proportion of studies with the true effect size is more than 70% and the unmeasured confounding needed to attenuate the effect is stronger than 1.5. The degree to which the lines are in the right upper quadrant (green area) indicates the that a causal association is more likely.

For cancer incidence, with an unmeasured confounding of 1.5, more than 70% of studies had a true effect size larger than a RR of 1.5 for liver and pancreatic cancer; larger than 1.3 for endometrial cancer; larger than 1.2 for gallbladder cancer; and larger than 1.0 for kidney, colon, colorectal, rectum and thyroid cancer. For stomach, leukemia, bladder, ovarian, non-Hodgkin's lymphoma (NHL), breast, melanoma, lung, esophagus, and prostate cancers, the proportions were lower than 70% assuming a true effect size stronger than 1.0 and an unmeasured confounding with a RR of 1.5. For pancreatic cancer mortality, with the same confounding strength, more than 70% of studies had an effect size larger than 1.3.

Figure 3 presents the estimated proportion of studies with a 10% and 30% increased risk of outcome (or corresponding decreased risk of prostate cancer incidence) under an unmeasured confounding strength of 1.5. Under this assumption, the proportion of studies with a true effect size larger than a RR of 1.1 (i.e., 10% increased risk in individuals with T2D) was 98% (95% CI 94, 100%) for liver, 97% (92, 100%) for pancreatic, 94% (78, 100%) for endometrial, 86% (64, 100%) for gallbladder, 67% (43, 91%) for kidney, 64% (45, 83%) for colon, 62% (48, 77%) for colorectal, 48% (23, 75%) for rectum, 44% (25, 62%) for stomach, 39% (20, 58%) for bladder, 33% (0, 66%) for leukemia, 32% (0, 72%) for thyroid, 24% (0, 53%) for ovarian, 24% (0, 49%) for NHL, 16% (0, 35%) for esophagus, 12% (0, 24%) for lung, 8% (0, 20%) for breast, and 3% (0, 22%) for melanoma cancer incidence (Fig. 3). For a true effect size larger than a RR of 1.3 (30% increased risk), estimates were 92% (84, 100%) for liver, 90% (80, 99%) for pancreatic, 72% (44, 100%) for endometrial, 65% (37, 92%) for gallbladder, and less than 25% for other cancers incidence. For a 10% and 30% decreased risk of prostate cancer incidence in people with T2D, proportions were 37% (20, 54%) and 1% (0, 4%), respectively (Fig. 3). For pancreatic cancer mortality, assuming the same strength of unmeasured confounding of 1.5, the proportions of studies with a true effect size larger than a RR of 1.1 and 1.3 were 92% (68, 100%) and 73% (34, 100%), respectively (Fig. 3). Bias analyses restricted to the 120 cohorts with adequate outcome assessment and follow-up are shown in Supplementary Tables 5 and 6. The results were consistent with those of the main analysis, except for the lower proportions of studies with true effect size stronger than 1.1 and 1.3 for endometrial cancer incidence—10% risk: 94% in the

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

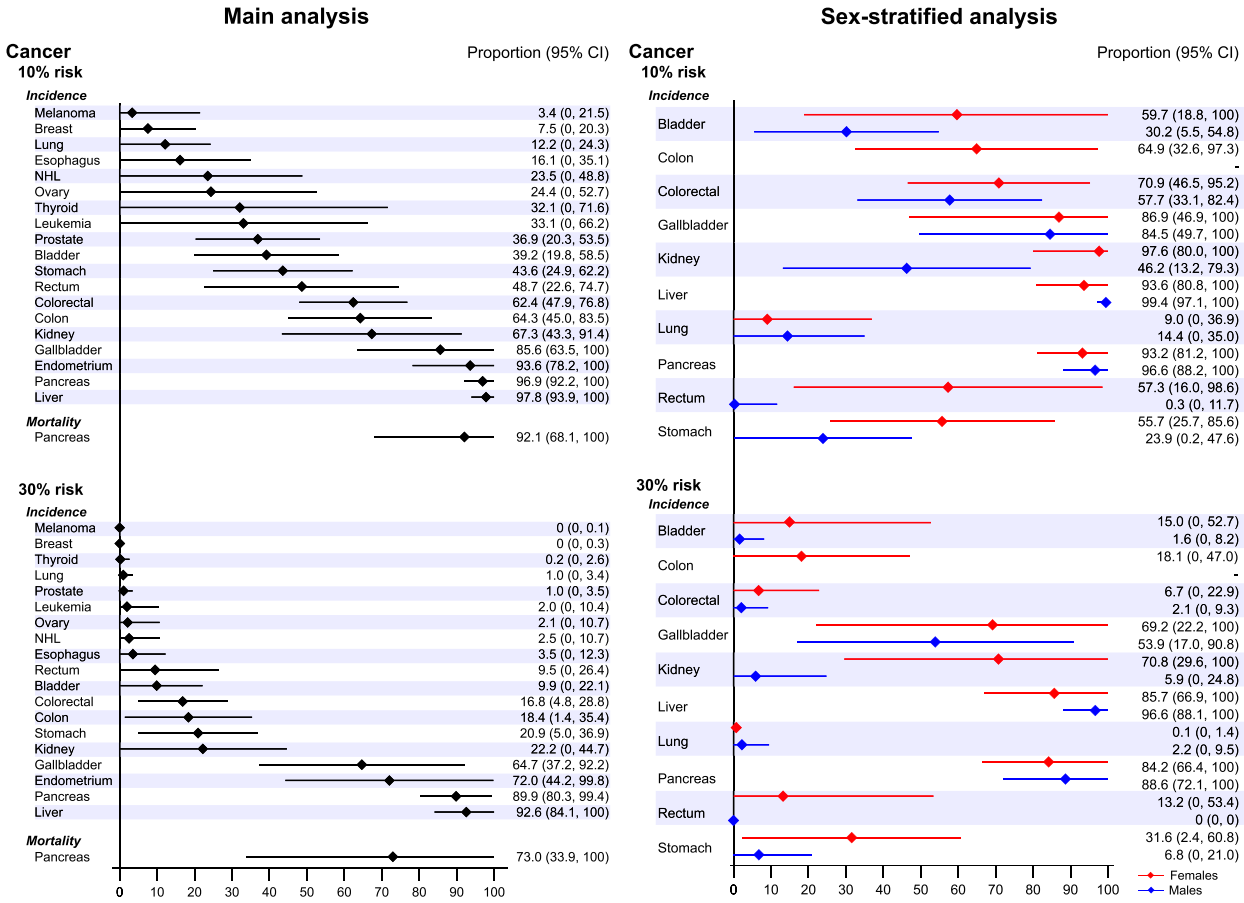

Figure 3—Proportions of studies with an unconfounded association of T2D with cancer. Estimated proportions of studies with a 10% and 30% increased risk (or reduced risk for prostate cancer) under an unmeasured confounding strength of 1.5. A 10% risk indicates a prespecified RR in people with T2D of 1.1 (or 0.9 for prostate cancer incidence), and a 30% risk indicates a prespecified RR in people with T2D of 1.3 (or 0.7 for prostate cancer incidence). Bars indicate 95% CI.

main analysis versus 80% in the restricted analysis; 30% risk: 72% in the main analysis versus 55% in the restricted analysis.

Supplementary Fig. 9 shows the strength of unmeasured confounding needed to reduce the proportion of studies, with the true effect size stronger than various prespecified RRs, to values lower than 70% and 90%. The strength of unmeasured confounding needed to nullify the association between T2D and cancer (i.e., to reduce the proportion of studies with an true effect larger than a prespecified RR of 1.0 to a value lower than 70%) ranged from 3.3 for liver cancer to 1.1 for melanoma cancer incidence and 2.4 for pancreatic cancer mortality (Supplementary Fig. 9). Corresponding estimates to reduce the proportion to a value lower than 90% were 2.4 for liver cancer and 1.0 (i.e., no further confounding was needed) for melanoma cancer incidence and 1.9 for pancreatic cancer mortality (Supplementary Fig. 9).

DISCUSSION

Using cohort-level data, this meta-analysis summarized the associations between T2D and cancer incidence and mortality and, in a bias analysis, quantified the robustness of the observational associations to unmeasured confounding to estimate the likelihood of causality. The results, obtained from 151 cohorts reporting data on 32 million people, more than 1.1 million cancer incidence events and 150,000 cancer deaths, indicated that people with T2D have a 15–25% higher risk of all-site cancer incidence and mortality compared with those without. In particular, T2D was associated with a decreased risk of prostate cancer incidence; an increased risk of breast, NHL, ovarian, bladder, leukemia, stomach, thyroid, rectum, colorectal, colon, kidney, gallbladder, endometrial, pancreatic, and liver cancer incidence; and pancreatic cancer mortality. Conversely, there was no clear evidence of associations with melanoma, esophagus, or lung cancer incidence. The bias analyses for unmeasured confounding were strongly suggestive for causal associations between T2D and liver, pancreatic, and endometrial cancer incidence, and pancreatic cancer mortality; the association with gallbladder cancer incidence was likely to be causal; associations with kidney, colorectal, and thyroid cancer incidence were less robust to unmeasured confounding; while the association with leukemia, prostate, breast, bladder, stomach, ovarian, NHL, melanoma, lung, or esophageal cancer was unlikely to be causal.

Although causal inference using observational studies is weaker than that obtained from randomized controlled experiments (i.e., randomized controlled trials), in recent years there has been an increasing interest on inferring causality from nonrandomized studies because

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

randomized experiments are not always possible (23). Alongside the methodology of Mendelian randomization, which presents some important challenges to infer causality from observational data (24,25), bias analysis for unmeasured confounding, in both single observational studies and meta-analyses, allowed to assess the strength of causal evidence by estimating how robust the associations are to unmeasured confounding (9,10).

Previous systematic reviews and meta-analyses exploring the association between T2D and cancer have shown an increased risk for many (26–29), but not all (30,31), cancers. These findings are generally consistent with ours. However, our analysis included more recent studies; excluded nonlongitudinal studies; and used the Knapp and Hartung method which has been suggested in random-effects meta-analyses with high heterogeneity across studies (17). In an umbrella review including 18 meta-analyses (4), one of the few studies that assessed the potential bias in the association between diabetes and cancer, the authors estimated cancer-specific 95% prediction intervals, which predicted the potential effect of the exposure in a future individual study setting (32,33). Of the 27 prediction intervals reported, only four excluded the null value (breast, intrahepatic cholangiocarcinoma, colorectal, and endometrial cancer incidence) (4). These results are to some extent in line with our findings, except for breast and pancreatic cancer. However, the bias analysis we used in this study enabled to quantify the proportions of studies with a true (causal) effect for different values of prespecified risk and a range of values of unmeasured confounding (9,20,34), giving the possibility to assess the strength of causal evidence under different assumptions.

T2D and cancer share several common risk factors, such as ageing, obesity, unhealthy diet, physical inactivity, alcohol, and smoking (35). The association between T2D and cancer observed in epidemiological studies may be confounded by these factors, although more recent studies included in our analysis have accounted for these confounders, particularly BMI (20). Our findings indicated that the strength of the association of T2D with several cancers, including breast, ovarian, bladder, or stomach, was not robust enough to unmeasured confounding.

T2D increases the risk of cancer via multiple potential biological mechanisms. While a direct effect of hyperglycemia is possible and supported by the evidence of an association between type 1 diabetes and cancer (36), the indirect effects of hyperinsulinemia, insulin resistance, chronic inflammation, and hormones imbalance have also been suggested as contributing factors (20,35). Mendelian randomization studies have showed that genetically predicted high insulin levels and obesity, but not diabetes, were associated with breast, endometrial, and pancreatic cancer incidence (37–39). These findings are in contrast with some of our results. However, rather than completely contradicting the association of T2D with cancer observed in epidemiological studies, Mendelian randomization studies could suggest that the relative contribution of insulin-related and hyperglycemia-related mechanisms may differ for different cancers (38). Other possible explanations are the potential violation of the assumptions in the Mendelian randomization or the larger statistical power (sample size) required to detect the relatively small effect of T2D-related genetic variants on cancer outcomes (37–40). Of note, our analyses confirmed the inverse association between T2D and prostate cancer incidence, which has been reported in several studies, yet the mechanisms underlying this relation remain unclear (from the lower androgen levels in individuals with diabetes to the protective effects of some diabetes medications) (41). In this regard, the uncertainty about biological plausibility concurs with the results of this bias analysis, suggesting that the association could be subject to unmeasured confounding.

Although our analyses reaffirmed the robust evidence for a causative association between T2D and liver, pancreatic, and endometrial cancer, it remains unclear which characteristics of diabetes are (most) accountable for such an increased risk. In view of the complex metabolic and clinical nature of T2D, several factors of T2D may increase the risk of cancer. An earlier diagnosis of T2D and an improved management of cardiovascular risk factors have resulted in a longer life expectancy in people with T2D (42–44), with the consequent longer exposure to the detrimental effects of hyperglycemia, insulin resistance, and chronic inflammation, all potentially associated with an increased risk of cancer (45). As most of the included studies used a prevalent cohort design, people with T2D in the current analysis were at different stages of diabetes with variable duration, resulting in the inclusion of individuals with heterogeneous phenotypes of insulin resistance and β-cell dysfunction during the dynamic changes of hyperglycemia in T2D (1). This may contribute to the heterogeneity observed in our meta-analyses for several cancer outcomes, in view of the role of hyperinsulinemia on cell proliferation (45). Another emerging area is the potential impact of glucose-lowering pharmacotherapy on cancer risk, with some medications showing an increased risk of cancer (20). Further to the aforementioned mechanisms linking T2D to cancer incidence, other factors should be considered in the relationship between T2D and cancer mortality. Cancer treatments, for example, should be based on the presence of cardiovascular and renal complications (46), which are more frequent in individuals with T2D. Moreover, the comparative contribution of the biological mechanisms linking T2D to cancer incidence and mortality is likely different: while a prolonged status of insulin resistance contributes mainly to an increased risk of cancer incidence, this pathophysiological abnormality may be less relevant, compared with hyperglycemia, in the relationship between T2D and cancer mortality (47). These pathophysiological factors may also act differently for each cancer. Therefore, future individual-level studies with detailed information on diabetes duration, therapy, and dynamic glycemic control are warranted to investigate their respective roles in cancer development and mortality.

To our knowledge, this is the first study investigating the robustness of the association between T2D and cancer using a bias analysis for unmeasured confounding. Another major strength is the extensive search in multiple electronic databases, the inclusion of only longitudinal studies, and the exclusions of overlapping cohorts result in less biased estimates.

This study has also some limitations. We only included articles published in English, and most were from high-income countries; however, no clear evidence of publication bias was observed.

Second, for most outcomes, we observed significant statistical heterogeneity

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

across studies, which could be related to methodological and clinical diversity (48), such as variability in study design, outcome assessment, or definition and ascertainment of diabetes (i.e., discharge codes, laboratory tests, self-reported, prescriptions of glucose-lowering drugs). We used a random-effects meta-analysis with the Knapp-Hartung method to better account for such heterogeneity and to give a more robust inference about the strength of causal evidence in potentially heterogeneous studies (9,49). Nonetheless, our results should be interpreted alongside other potential study-level sources of bias, such as indication bias, selection bias, and measurement errors. Furthermore, it has been argued that the reported associations between T2D and cancer may be exaggerated due to potential reverse causality, particularly pancreatic cancer, with hyperglycemia often being the initial clinical sign of this cancer (26). Detection bias may also occur, especially during the period shortly after the onset of diabetes, as individuals with T2D may have more frequent disease surveillance (50). To rule out reverse causality and detection bias, some studies excluded outcomes which occurred during the first few years of follow-up. In addition, we have conducted analyses restricted to studies with adequate outcome assessment and follow-up, to minimize the potential impact of reverse causality and detection bias, showing consistent results.

Third, though we excluded studies comprising only individuals with type 1 diabetes, some cohorts did not distinguish between type 1 and type 2 diabetes in the inclusion criteria; however, the proportion of people with type 1 diabetes in the cohorts was likely very small.

Lastly, although the risk factors and the biology of cancer of the same anatomical location may differ (e.g., squamous cell versus esophageal adenocarcinoma), detailed histopathological characteristics were not available in most of the included studies.

In summary, the results of this quantitative synthesis of cohort-level data suggest a very likely causal relationship between T2D and liver, pancreatic, and endometrial cancer incidence, and pancreatic cancer mortality, and a likely causal association with gallbladder cancer incidence. While the associations with kidney, thyroid, and colorectal cancer incidence were less robust to unmeasured confounding, we did not find evidence of causal relationships for other cancers. The stage at which cancer is diagnosed is a strong determinant of its outcome, with treatment options and long-term survival being much greater for early stage localized disease (8). There is certainly scope for improving outcomes by detecting cancer earlier in individuals with T2D. In the U.K. general population, for example, over half of colorectal and 80% of pancreatic cancers are diagnosed at a late stage (51). Furthermore, a better understanding of T2D-related causal factors for specific cancers, such as glucose-lowering treatments, glucose control, and diabetes durations, should lead to a more cohesive public health message around T2D-related complications that include cancer alongside cardiovascular disease, of which there is far greater awareness.

Funding. S.L., J.K.M., K.K., and F.Z. are part of the Leicester Real World Evidence Unit, which is funded by University of Leicester NIHR Applied Research Collaboration East Midlands (ARC-EM) and Leicester Biomedical Research Centre. This project was supported by the Leicester Institute of Advanced Studies (Tiger team).

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Duality of Interest. K.K. has received honoraria and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, and Sanofi outside of the submitted work. M.J.D. has acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Janssen; an advisory board member for Servier; a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc.; and has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi–Aventis, Lilly, Boehringer Ingelheim, and Janssen outside of the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.L. contributed to the concept, design, data extraction, analysis and interpretation of the data, and the first draft. K.B., J.K.M., L.H., A.M., and E.I. contributed to the data extraction and critical revision of the article. T.Y., K.K., and M.J.D. contributed to the interpretation of the data and critical revision of the article. F.Z. contributed to the concept, design, data extraction, interpretation of the data, critical revision of the article, and study supervision. S.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. Postgrad Med J 2016;92:63–69

2. International Diabetes Federation. IDF Diabetes Atlas 8th edition 2017 [Internet], 2020. Available from https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html. Accessed 20 April 2020

3. Tancredi M, Rosengren A, Svensson A-M, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732

4. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607

5. Ohkuma T, Peters SAE, Woodward M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. Diabetologia 2018;61:2140–2154

6. Abarca-Gómez L, Abdeen ZA, Hamid ZA, et al.; NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017;390:2627–2642

7. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol 2011;8:228–236

8. Hiom SC. Diagnosing cancer earlier: reviewing the evidence for improving cancer survival. Br J Cancer 2015;112(Suppl. 1):S1–S5

9. Mathur MB, VanderWeele TJ. Sensitivity analysis for unmeasured confounding in meta-analyses. J Am Stat Assoc 2020;115:163–172

10. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–274

11. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533

12. Morrison AE, Zaccardi F, Khunti K, Davies MJ. Causality between non-alcoholic fatty liver disease and risk of cardiovascular disease and type 2 diabetes: a meta-analysis with bias analysis. Liver Int 2019;39:557–567

13. Baumeister SE, Leitzmann MF, Linseisen J, Schlesinger S. Physical activity and the risk of liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis. J Natl Cancer Inst 2019;111:1142–1151

14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700

15. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. Am J Epidemiol 1982;116:547–553

16. Wells G, Shea B, O'connell D, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa, Canada, Ottawa Hospital Research Institute, 2011

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024

17. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693–710
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539–1558
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634
20. García-Jiménez C, Gutiérrez-Salmerón M, Chocarro-Calvo A, García-Martinez JM, Castaño A, De la Vieja A. From obesity to diabetes and cancer: epidemiological links and role of therapies. Br J Cancer 2016;114:716–722
21. Ling S. Bias analysis results for diabetes and cancer [Internet]. Available from https://github.com/supingling/BiasAnalysis. Accessed 15 June 2020
22. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:48
23. Hernán MA. *JM R: Causal Inference: What If*. Boca Raton, FL, Chapman & Hall/CRC, 2020
24. VanderWeele TJ, Tchetgen Tchetgen EJ, Cornelis M, Kraft P. Methodological challenges in mendelian randomization. Epidemiology 2014;25:427–435
25. Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. Nat Rev Cardiol 2017;14:577–590
26. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076–2083
27. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. Diabetologia 2011;54:1013–1018
28. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679–1687
29. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007;121:856–862
30. Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer Prostatic Dis 2013;16:151–158
31. Lee J-Y, Jeon I, Lee JM, Yoon J-M, Park SM. Diabetes mellitus as an independent risk factor for lung cancer: a meta-analysis of observational studies. Eur J Cancer 2013;49:2411–2423
32. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342: d549
33. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172:137–159
34. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. Epidemiology 2016;27: 368–377
35. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin 2010;60:207–221
36. Sona MF, Myung SK, Park K, Jargalsaikhan G. Type 1 diabetes mellitus and risk of cancer: a meta-analysis of observational studies. Jpn J Clin Oncol 2018;48:426–433
37. Carreras-Torres R, Johansson M, Gaborieau V, et al. The role of obesity, type 2 diabetes, and metabolic factors in pancreatic cancer: a Mendelian randomization study. J Natl Cancer Inst 2017;109: djx012
38. Nead KT, Sharp SJ, Thompson DJ, et al.; Australian National Endometrial Cancer Study Group (ANECS). Evidence of a causal association between insulinemia and endometrial cancer: a mendelian randomization analysis. J Natl Cancer Inst 2015;107:djv178
39. Goto A, Yamaji T, Sawada N, et al. Diabetes and cancer risk: a Mendelian randomization study. Int J Cancer 2020;146:712–719
40. Burgess S. Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome. Int J Epidemiol 2014;43:922–929
41. Pierce BL. Why are diabetics at reduced risk for prostate cancer? A review of the epidemiologic evidence. Urol Oncol 2012;30:735–743
42. Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KM, Thompson TJ. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985-2011: a modelling study. Lancet Diabetes Endocrinol 2014;2:867–874
43. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523
44. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376: 1407–1418
45. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci 2013;104:9–14
46. Richardson LC, Pollack LA. Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol 2005;2:48–53
47. Ramteke P, Deb A, Shepal V, Bhat MK. Hyperglycemia associated metabolic and molecular alterations in cancer risk, progression, treatment, and mortality. Cancers (Basel) 2019;11: 1402
48. Higgins J, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions, version 6 [Internet], 20019. Available from https://training.cochrane.org/handbook/current. Accessed 18 June 2020
49. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med 2014;160:267–270
50. Colmers IN, Majumdar SR, Yasui Y, Bowker SL, Marra CA, Johnson JA. Detection bias and overestimation of bladder cancer risk in type 2 diabetes: a matched cohort study. Diabetes Care 2013;36:3070–3075
51. Cancer Statistics for the UK [Internet], 2019. Available from https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk. Accessed 18 November 2019

Downloaded from http://ada.silverchair.com/care/article-pdf/43/9/2313/629815/dc200204.pdf by guest on 10 April 2024