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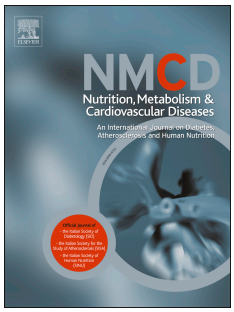

Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts

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Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts

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Abstract

Introduction: Whether the relative risk of cancer incidence and mortality associated with diabetes has changed over time is unknown.

Methods: On August 12th, 2020, we electronically searched for observational studies reporting on the association between diabetes and cancer. We estimated temporal trends in the relative risk of cancer incidence or mortality associated with diabetes and calculated the ratio of relative risk (RRR) comparing different periods.

Results: 193 eligible articles, reporting data on 203 cohorts (56,852,381 participants; 3,735,564 incident cancer cases; 185,404 cancer deaths) and covering the period 1951-2013, were included. The relative risk of all–site cancer incidence increased between 1980 and 2000 [RRR 1990 vs.1980: (1.24; 95% CI: 1.16, 1.34); 2000 vs.1990: (1.23; 1.15, 1.31)] and stabilised thereafter at a relative risk of 1.2; the relative risk of all–site cancer mortality was constant at about 1.2 from 1980 to 2010. Both magnitudes and trends in relative risk varied across cancer sites: the relative risk of colorectal, female breast, and endometrial cancer incidence and pancreatic cancer mortality was constant during the observed years; it increased for bladder, stomach, kidney, and pancreatic cancer incidence until 2000; and decreased for liver while increased for prostate, colon and gallbladder cancer incidence after 2000.

Conclusions: Alongside the increasing prevalence of diabetes, the temporal patterns of the relative risk of cancer associated with diabetes may have contributed to the current burden of cancer in people with diabetes.

Keywords: diabetes; trend analysis; relative risk; systematic review; cancer

Introduction

Individuals with diabetes have a higher risk of premature death,[1, 2] which is mainly attributed to an increased incidence of cardiovascular disease (CVD) complications.[2-4] In the last few decades, however, accumulating evidence also indicates an increased risk of some cancer incidence and mortality in individuals with diabetes,[5, 6] likely to a greater extent in women than in men.[7, 8]

The population attributable fraction, an epidemiologic measure of public health impact of an exposure, is quantified by the prevalence of the exposure and the relative risk of the association between the exposure and the outcome.[9] A recent report estimated, worldwide, approximately 290,000 new cancer cases (2% of all incident cases) attributable to diabetes in 2012, of which a quarter were related to the increasing prevalence of diabetes since the 1980s:[10] these estimates only accounted for the increasing prevalence of diabetes while assuming a constant relative risk of cancer incidence associated with diabetes. However, whether the relative risk of cancer incidence or mortality has been stable during the last few decades is unknown, whereas previous studies have shown a declining relative risk of CVD hospitalisation or mortality comparing people with vs without diabetes.[11-13]

Along with the global increase in the prevalence of diabetes,[14] an increase in the relative risk of cancer associated with diabetes may have contributed to the contemporary burden of cancer in people with diabetes. In this study, we aimed to investigate temporal trends in the relative risk of all–site and site–specific cancer incidence and mortality associated with diabetes.

Methods

Data sources and Searches

An umbrella review on the evidence about type 2 diabetes and risk of cancer incidence and mortality was published in 2015, which included previous relevant meta–analyses of observational studies up to December 2013.[6] We updated the systematic search by querying PubMed, Web of Science and the Cochrane Library of Systematic Reviews for systematic reviews and observational studies reporting on the association between diabetes and cancer incidence or mortality published between 1st December 2013 and 12th August 2020. The search algorithm is shown in Supplementary Material Figure S1. Three reviewers (SL, AM, FZ) screened titles and abstracts; bibliographies of all meta–analyses (including the umbrella review) were manually reviewed (SL, KB, AM, LH, EI, FZ). Articles with any uncertainties at this stage were included for further examinations. We followed the PRISMA guidelines in reporting this systematic review.[15]

Study selection

Articles were eligible if they reported the start and end of follow–up and estimates, with corresponding 95% confidence intervals (CIs) or standard errors (SEs) or p–values, for the longitudinal association between diabetes and cancer incidence or mortality; following rare disease assumption, rate ratio, hazard ratio, and odds ratio were assumed to approximate the same measure of relative risk.[16] Articles reporting age– (and sex–) standardised incidence ratio (SIR) or standardised mortality ratio (SMR) comparing people with diabetes to local/national/worldwide general populations were also included but analysed separately. Studies were excluded if: 1) the cohort focused on some specific populations (e.g., patients with cancer; patients with hepatitis B or C for liver cancer outcome); 2) the exposure of

interest was not type 2 diabetes (e.g., explicit type 1 diabetes only); 3) the outcome was not cancer incidence or mortality (e.g., adenoma). In the case of several cohorts reported in one article, all cohorts were included and recorded as distinct cohorts if information on follow–ups and estimates were available for each cohort, and data were extracted separately. In case of reports identified from the same database with no overlapping population or calendar years of follow–up, we considered them as distinct cohorts; while, in case of duplicate reports from the same cohort, we included that with the larger person–time–at–risk.

Data extraction and Quality assessment

For each included cohort, a standardised form was used to extract data on age, follow–up duration, body mass index, definition and ascertainment of exposure and outcomes, confounders, outcome–specific number of events and participants, person–years, and the most adjusted estimates. Quality of studies was assessed with the Newcastle–Ottawa Scale (NOS) for cohort studies.[17] The NOS score ranges from 0 to 9, with a higher score indicating the higher quality of the study, and is the sum of the score for three items: selection of the participants (0–4); comparability between exposed and non–exposed participants (0–2); and assessment of outcome and adequacy of follow–up (0–3). We considered age and body mass index as the most relevant confounding factors, 5 years as adequate follow–up durations, and 90% as adequate follow–up rates.

Data analysis

We calculated the study mid–year based on the start and end year of the follow–up, with the following equation: *mid–year = [(cohort recruitment start year + cohort recruitment end year)/2 + follow up end year]/2*. If estimates were stratified (e.g., by age groups or gender),

an overall within–cohort pooled effect was calculated with a fixed–effect meta–analysis. Our primary analyses sought to estimate trends in relative risk (or SIR/SMR) of cancer incidence and mortality associated with diabetes, by cancer sites and in both genders. To include the largest set of individuals, studies that only reported on one gender were also comprised in our primary analyses. Estimates were also reported, where possible, separately by gender and geographical regions (Europe and Middle East, North America, and Asia).

For each trend analysis, we first tested for non–linearity in the relationship between the most–adjusted relative risk (or SIR/SMR) and the calendar mid–year by comparing two linear regressions: one with restricted cubic splines (RCS) of mid–year and one with a single linear term; both regressions were weighted by the inverse of the variance of the cohort–specific estimate. As the number of studies for each outcome is relatively small (<100), RCS models used 3 knots to avoid over–fitting,[18] and the analyses were only performed for outcomes with at least 5 cohorts. The Akaike Information Criterion (AIC) indicated that for all regression non–linear models were better (i.e., lower AIC), the non–linear models were then used to estimate the trends of relative risk (or SIR/SMR) across calendar time. Based on the availability of data over time, we also calculated the ratio of these relative risk (RRR) comparing the relative risk of cancer associated with diabetes by every decade (i.e., 1980 vs. 1990; 2000 vs. 1990; 2010 vs. 2000, where possible); a RRR >1 indicates that the relative risk associated with diabetes is greater than of the reference year (e.g. in 2010 vs. 2000, a RRR>1 indicates the RR is greater in 2010 than 2000).[19]

Analyses were conducted in R for Windows (version 3.6.1) using the ‘rms’ package[20] and results are reported with 95% confidence intervals (CIs). Data manipulation and graph preparation were done in Stata/IC 16.1 (StataCorp, College Station, TX).

Results

Characteristics of included studies

The systematic search identified 2930 citations; after screening of titles and abstracts, 138 observational studies and 49 meta–analyses (including the umbrella review) were deemed relevant and eligible for further assessment (Figure S1). The manual review of references of the meta–analyses identified further 260 observational studies after removing duplicates. Of the 398 articles with full–text assessment, 205 were excluded (reasons are reported in Supplementary Material Table S1); the remaining 193 articles, with information on 203 cohorts, 56,852,381 participants; 3,735,564 incident cancer cases; 185,404 cancer deaths, were included in the analyses. References of the 193 included articles are reported in the Supplementary Material.

The characteristics of the included cohorts are shown in Table S2; the quality of the included cohorts was medium to high, with NOS score ranging from 4 to 9 (out of 9) and a median of 7 (Table S3). Of the 203 included cohorts, 171 reported relative risk (144 on incidence and 33 on mortality) and 32 reported SIR or SMR (31 on incidence and 14 on mortality). Overall, the incidences of colorectal, all–site, pancreas, liver and lung cancer were most frequently reported; for mortality, all–site, pancreas, liver, stomach and lung cancer were most frequently reported (Figure S2 and Figure S3). The mid–years covered approximately 60 years, from 1951 to 2013, with the number of studies on diabetes and cancer having rapidly increased since the 1990s (Figure S4).

Trends in the relative risk of cancer associated with diabetes

Cancer incidence

There were 144 cohorts reporting relative risk of diabetes–associated cancer incidence, with modelled trends available for all–site (n=33) and 19 distinct cancer sites, ranging from 49 cohorts for colorectal cancer to 13 cohorts for leukaemia (Figure 1).

The relative risk of all–site cancer incidence increased from 1980 and subsequently levelled off from year 2000, with a relative risk of approximately 1.2 thereafter (Figure 1). The RRR was 1.24 (95% CI: 1.16, 1.34) comparing 1990 to 1980; 1.23 (1.15, 1.31) comparing 2000 to 1990; and 1.06 (0.99, 1.13) comparing 2010 to 2000 (Figure 2).

Trends in the relative risk of site–specific cancer incidence were mainly available between 1980 and 2013, with less precise or no estimates before 1990; both trends and magnitudes of relative risk varied across cancer sites (Figure 1). Diabetes was associated with a rather stable increased risk of colorectal (relative risk about 1.2), female breast (1.1), rectum (1.2) and endometrial (1.5) cancer. Trends in the relative risk of pancreatic, bladder, stomach and kidney cancer incidence were mirrored by that of all–site cancer, as they increased before 2000 and stabilised thereafter at a relative risk of 2.0, 1.2, 1.2, and 1.4, respectively, until 2010. Conversely, diabetes was associated with a rather stable lower risk of prostate cancer (relative risk 0.8) before 2000, followed by an increasing trend leading to a null association in more recent years (Figure 1). The relative risks of colon (1.2), gallbladder (1.3), and liver (2.0) cancer incidence were constant before 2000; thereafter, they increased for colon and gallbladder but decreased for liver, resulting in about 1.5, 2.0, and 1.5 in 2010, respectively (Figure 1).

Correspondingly, the RRR was 1.62 (1.21, 2.16) for pancreatic cancer comparing 1990 to 1980 (Figure 2); 1.49 (1.18, 1.88) for pancreatic, 1.18 (1.07, 1.30) for bladder, 1.22 (1.02, 1.46) for stomach, and 1.31 (1.14, 1.50) for kidney cancer comparing 2000 to 1990; and 1.20 (1.07, 1.35) for prostate, 0.74 (0.63, 0.87) for liver, 1.09 (0.99, 1.20) for bladder, 1.25 (1.10,

1.43) for colon, and 1.64 (1.20, 2.25) for gallbladder cancer comparing 2010 to 2000 (Figure 2).

Stratified analyses by sex were possible for all–site cancer in men and women, 15 cancer sites in men, and 11 cancer sites in women (Figure S5 and Figure S6). Overall, there were more cancer sites with increasing trends in the relative risk in men than women, including all–site, bladder, esophagus, and gallbladder cancer (Figure S7). Separate results by geographical regions are shown in Figures S8–S10, with all–site cancer available in all three regions, and 19, 11, and 11 site–specific cancers available in Europe and Middle East, North America, and Asia and Australia, respectively. In addition, only 31 cohorts reported data on SIR, resulting in modelled estimates with larger uncertainties; overall and sex–stratified estimates are shown in Figure S11 and S12, respectively.

Cancer mortality

For cancer mortality, 33 and 14 cohorts reported estimates as relative risk and SMR, respectively. Among studies reporting the relative risk, the available number of studies allowed trend analyses for all–site, female breast, colorectal, esophagus, lung, pancreas, prostate, and stomach cancer; for those reporting SMRs, they were possible for all–site, liver, lung, pancreas, prostate, and stomach cancer. Like incidence, estimates were more precise when combining relative risk than SMR (Figure S13). Between 1980 and 2010, diabetes was stably associated with a relative risk of about 1.7 for pancreatic cancer mortality and about 1.2 for all–site cancer mortality, and stable trends but borderline significant relative risks were also observed for other cancer sites (Figure S13). Given the very limited number of cohorts reporting SMR, although the observation was from year 1951, no clear trends could be visualised; yet, there was an increase in the SMR for all–site cancer mortality in recent

years (Figure S13). When stratified by women and men, large uncertainties limited the interpretation of the trends.

Discussion

Using study–level data, our systematic review examined trends in the relative risk of cancer incidence and mortality associated with diabetes. The relative risk of diabetes–associated all–site cancer incidence increased between 1980 and 2000, then stabilised thereafter at around 20% greater risk; for all–site cancer mortality, the risk was constantly 20% higher in people with diabetes from 1980 to 2010. For cancer–specific incidence or mortality, trends and magnitudes of relative risk associated with diabetes varied markedly by cancer sites. Specifically, the relative risk of pancreatic, bladder, stomach, and kidney cancer incidence showed a trend similar to all–site cancer incidence but with a greater risk; the relative risks for colorectal, female breast, and endometrial cancer incidence, and pancreatic cancer mortality were constant but with different magnitudes of the association. Lastly, the relative risk of prostate (0.8), colon, gallbladder, and liver (2.0) cancer incidence was rather stable before 2000 but decreased for liver and increased for prostate, colon, and gallbladder after 2000.

To our knowledge, only two observational studies have reported trends in the relative risk of cancer incidence associated with diabetes. Data from the Korean National Health Insurance indicated a stable trend in the incidence rate ratio for pancreatic cancer (about 1.4 in the whole population and 2.0 in middle-aged population) from 2006 and 2015.[21] Similarly, data from the UK Clinical Practice Research Datalink showed an unchanged relative risk from 1989 to 2012 with constant incidence rates in female breast cancer in people with and without diabetes.[22] These findings are in line with our results indicating a stable trend in the relative risk of breast and pancreatic cancer during the same period. In addition, our results of a stable but higher risk of cancer mortality in people with diabetes comparing to those without between 1980 and 2010 is consistent with previous observations from the

National Health Interview Survey in the US, showing a stable relative risk of cancer mortality (around 1.2 to 1.4) between 1988 and 2015.[12, 23, 24]

Although we did not specifically compare sex differences in the relative risk of cancer associated with diabetes, we observed more cancer sites with increasing trends in men than women, which we believe could be related to the larger number of cohorts with available data in men. However, sex differences in the association between diabetes and cancer have been already reported in some[7] but not all[8] previous study–level meta–analyses.

The biological mechanisms underlying the link between diabetes and cancer have been extensively studied. Hyperinsulinaemia, resulting from a compensatory effect to insulin resistance, stimulates mitogenesis;[25] the observation of an increased risk of cancer in type 1 diabetes also suggests a possible direct effect of hyperglycaemia on oncogenesis.[26] Furthermore, in the last few decades there has been an increase in the life expectancy (i.e., ageing) in individuals with type 2 diabetes in most Western countries, likely related to a better and wider treatment of cardiovascular risk factors which have resulted in downward mortality trends among people with diabetes,[11-13, 27-31] thus potentially leading to more years living with diabetes.[32] Although ageing itself is a risk factor for cancer, it should be noted that this demographic trends is combined with the epidemiological observation of the epidemic of obesity and insulin resistance in young children and young adults, resulting in an earlier onset of type 2 diabetes.[33] The two phenomena determine a longer exposure to insulin resistance, hyperinsulinaemia and hyperglycaemia: this may partly explain the increasing trends in the relative risk in some obesity–related cancers (e.g., colorectal, kidney, and gallbladder cancer) found in our study. The combined role of obesity/insulin resistance and hyperglycaemia on the risk of cancer is further supported by the epidemiological observation that three times more cancer cases can be attributed to the combined effect of diabetes and overweight compared to diabetes alone.[10] Of note, a poorer glycaemic control

and/or a greater exposure to hyperinsulinaemia in women may contribute to the biological mechanisms underpinning sex differences,[7] yet differences in other characteristics between men and women (i.e., age at diabetes diagnosis) may be the "true" reasons for differences in the sex-specific associations and trends, with sex being only a proxy of these characteristics.[34] We confirmed previous observations reporting a lower risk of prostate cancer incidence, variably attributed to a lower circulating levels of androgens or prostate-specific antigen in subjects with diabetes or to a possible antioncogenic effect of some glucose-lowering medications.[35] However, while noting a trend towards a null association in more recent years, residual confounding cannot be completely ruled out.[35]

Our findings have several important implications. First, in contrast to the declining relative risk reported for all–cause mortality, CVD–related mortality, and CVD hospitalizations,[11, 13, 23, 28, 30] the relative risk in cancer incidence and mortality comparing people with vs. without diabetes has been shown to be stable[12, 22, 36] and, in our study, increasing for some cancers; this indicated a potential shift in long–term diabetes–related complications, [36-38] in line with observations of a stable proportion of deaths related to cancer and declining proportion of deaths related to CVD in adults with diabetes.[23, 39, 40] Taken together, these changing trends suggest the relevance of cancer as a long–term diabetes–related complication, potentially leading to larger proportion of people with diabetes living with diabetes, CVD, and cancer.

Second, the absence of a decline in the relative risk of cancer incidence and mortality, unlike CVD, has also resulted in an increasing public health burden of cancer in people with diabetes, given the increasing prevalence of type 2 diabetes. Notably, the burden of colon and gallbladder cancer attributable to diabetes has increased during the last years not only as a consequence of an increasing prevalence of type 2 diabetes but also as an effect of increasing trends in the relative risk of developing these cancers in people with diabetes.[10, 41]

Third, there is currently lack of guidance on cancer screening in people with diabetes: current cancer screening strategies do not account for the presence of diabetes whilst opportunistic screening is left to decision of the individual healthcare professionals. This is in striking contrast with the numerous guidelines on CVD risk factors management in people with diabetes who, considered at higher risk of CVD, are routinely screened for risk factors (i.e., blood pressure, dyslipidaemia, or body mass index) or pre-clinical CVD (i.e., computed tomography coronary angiography). Our findings would suggest that a more tailored screening approach in subjects with diabetes, ranging from investigations at younger ages to more frequent assessments, could translate in an earlier cancer diagnosis and treatment and potentially a longer survival. These initiatives should also account for the differential magnitude of the associations with heterogeneous cancers (i.e., liver, pancreas, or kidney vs breast) and the contributing role of other factors associated with diabetes (i.e., earlier screening in subjects with diabetes and obesity). However, further research is required to clarify whether specific cancer screening strategies are required in people with diabetes, particularly for some types of cancer with increasing trends or higher relative risk. Similarly, there are numerous guidelines suggesting treatments of and targets for CVD risk factors specifically in people with diabetes (e.g., ACE–inhibitors among the antihypertensive medications and distinct targets for low–density–lipoprotein cholesterol reduction), while no indication is to date available for cancer treatments or glucose control specifically in cancer patients with diabetes; whether the treatments or follow–up in these patients should differ is another area of future investigation.

Our study has several limitations. First, trends were available for most cancer–specific incidence only after 1980, while limited number of cohorts reported data on cancer mortality, though it started from 1950; studies with longer follow–ups are needed to expand the observing calendar years. Second, most studies were from high–income countries, although

the number of studies from Asia is increasing and data quality is improving. No studies were identified from South Asia, South America, or Africa, limiting the generalisability of our results; given the faster increase in the prevalence of diabetes in these regions,[14] further analyses are required to detail trends in low– and middle–income countries. Third, the extent of adjustment differed across studies, yet most adjusted for age and half of them for body mass index; the relative risk of cancer may change by diabetes duration,[42, 43] which has not been accounted for in all studies; some glucose–lowering medications, including insulin, have been claimed to be associated with either increasing or decreasing risk of cancer:[44] this may have had an impact on the relationship, as the profile of glucose–lowering medications has changed in last few decades.[45] Fourth, cancer screening programs are different across countries and over time, thus influencing the ascertainment of the outcome;[46] similarly, the diagnostic and screening criteria for diabetes have changed over time,[47] leading to an earlier diagnosis of the exposure: of note, a longer time between diabetes diagnosis and cancer detection may result in an underestimation of the RRR in our analyses.

Other factors could, to different extent, have contributed to our results:[44] yet, as in all descriptive studies, our main goal was not to identify possible reasons for these population–wide, multifactorial phenomena. Analytical strategies are potentially available to explore sources of heterogeneity: they should nevertheless be interpreted at study–level, whereby associations may differ compared to those observed at individual–level (ecological bias). Therefore, rather than performing these analyses and speculate on possibly reasons, we underline that individual–level analysis is necessary to both confirm our findings and identify possible explanations (aetiological investigations).

In summary, in this study we observed increasing trends in the relative risk for all–site, bladder, stomach, kidney, and pancreatic cancer incidence before 2000; for colon and

gallbladder cancer incidence after 2000. Conversely, we find no evidence of changing trends in the relative risk of all–site or pancreatic cancer mortality between 1980 and 2010. These results, combined with the decline in CVD–related complications in people with diabetes, underline a change in the phenotype of diabetes–related complications, and potentially increase the proportion of people with diabetes living with multimorbidities, including CVD and cancer: national and international organisations should raise a greater awareness on diabetes as a risk factor not only for CVD but also for cancer, and further research should address whether specific cancer screening strategies or treatment are required in people with diabetes. Moreover, our findings suggest that the cancer burden attributable to diabetes may be the results not only of the rising prevalence of diabetes but, at least for some cancer sites, also of the increasing trends in the risk of cancer associated with diabetes.

List of abbreviations

RRR: ratio of relative risk; CVD: cardiovascular disease; CI: confidence interval; SE: standard error; SMR: standardised mortality ratio; SIR: standardised incidence ratio; NOS: Newcastle–Ottawa Scale; RCS: restricted cubic spline; AIC: Akaike Information Criterion

Contributions

SL: design, data extraction, analysis, interpretation and writing; KB: data extraction, interpretation, and critical revision; JKM, LH, AM, EI: data extraction and critical revision; TY, KK, MJD: interpretation and critical revision; FZ: concept, design, data extraction, interpretation, critical revision, and study supervision. All authors have agreed to the final submitted version.

Ethics statement

Informed consent was not required for this type of research as no individual–level data were involved in the analysis, and only published study–level data were used.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of interests

SL, KB, JKM, LH, AM, EI, TY, and FZ declare no conflict of interest relevant to this article. KK has received honoraria and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi. MJD has acted as 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 and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator–initiated trials from Novo Nordisk, Sanofi–Aventis, Lilly, Boehringer Ingelheim and Janssen.

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FIGURE LEGENDS

Figure 1: Relative risk on the association between diabetes and cancer incidence by calendar year

Legend:

Subtitles indicates: cancer site; number of cohorts; incident cases/participants. Cancers are ordered (left–right; top–bottom) by number of cohorts.

Y axis: Relative risk; **X axis**: Cohort mid–year; **blue line**: modelled relative risk; **light–blue area**: modelled 95%CI; **green dot**: study relative risk; **green line**: study relative risk 95%CI.

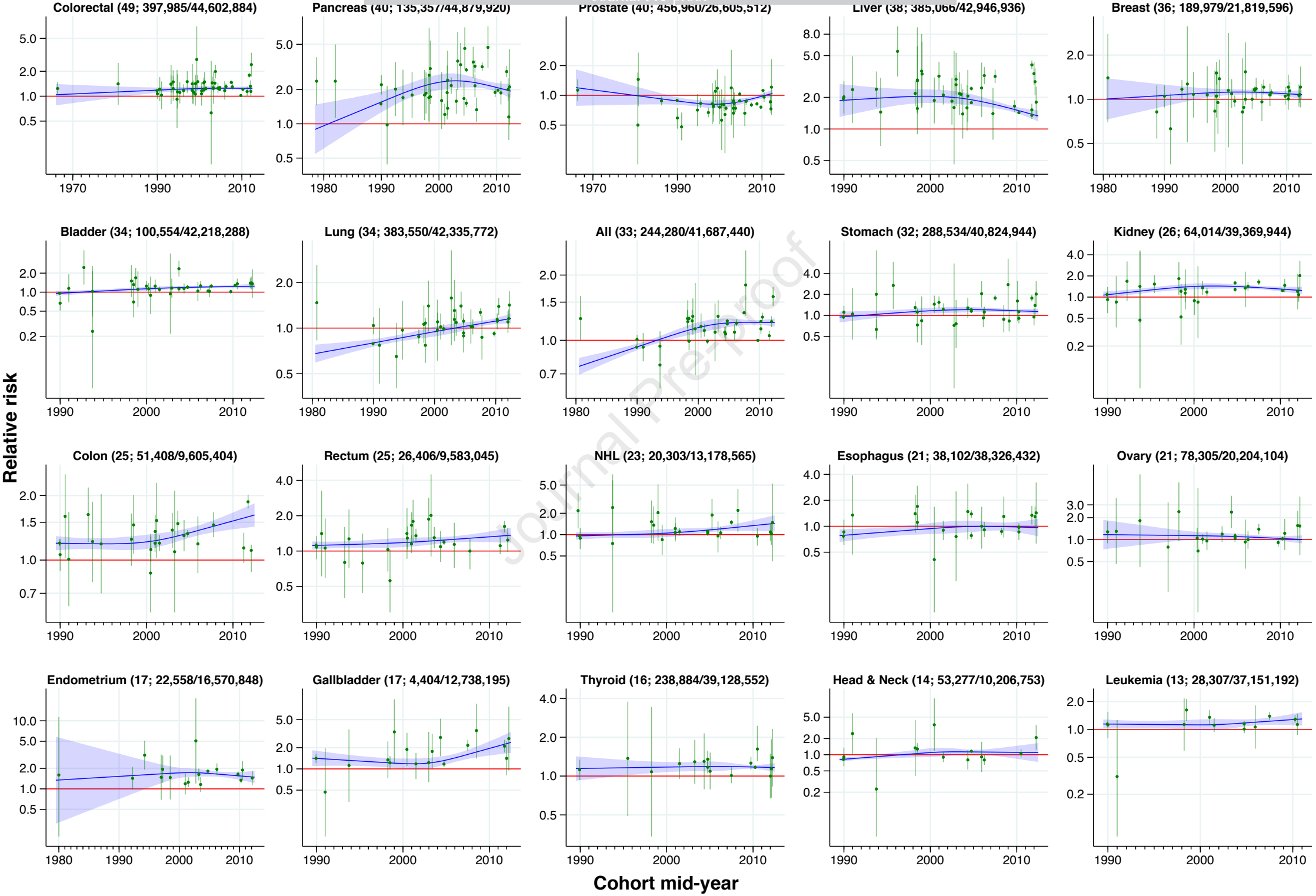
NHL: non–Hodgkin's lymphoma.

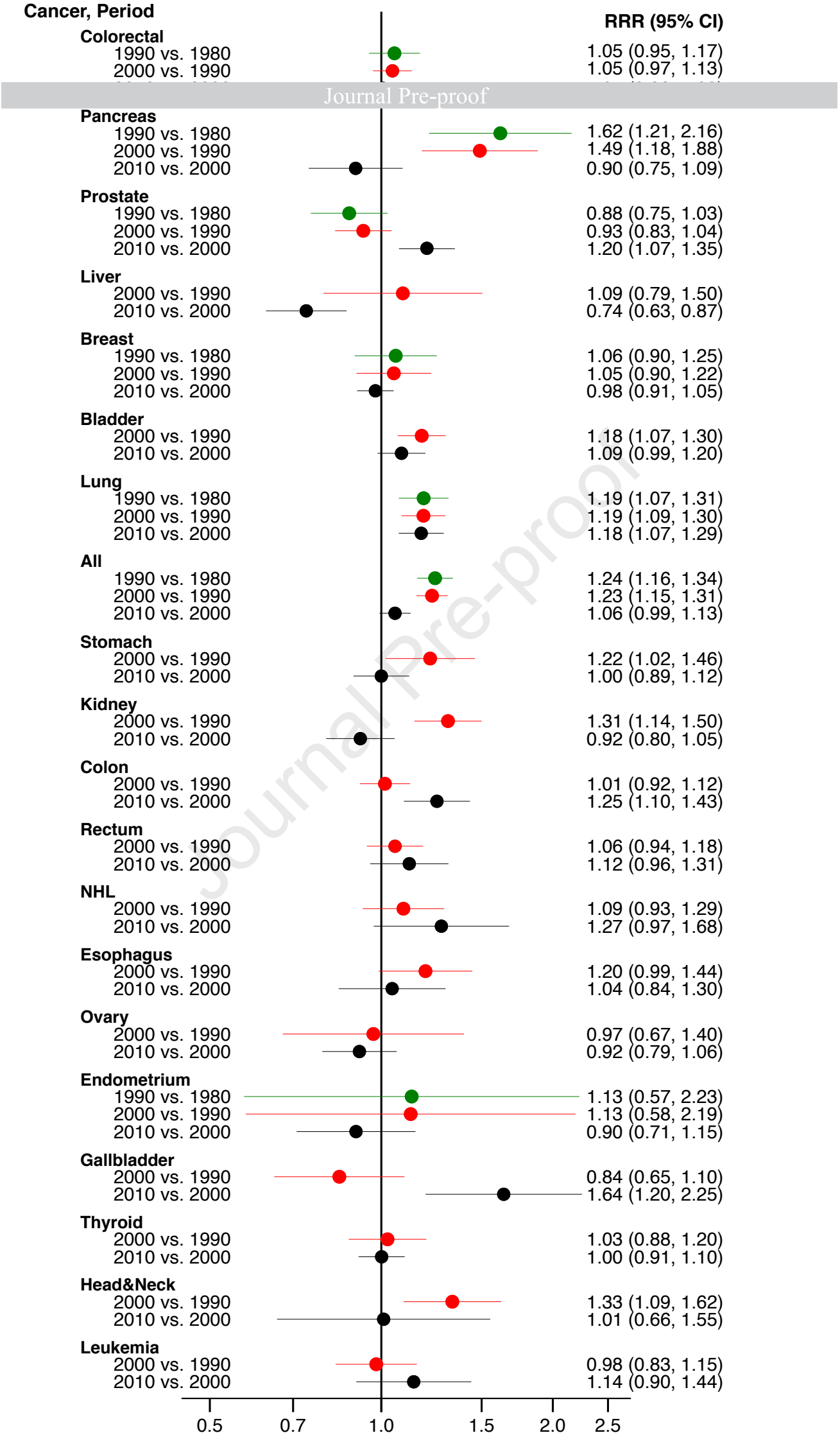
Figure 2: 10–year ratio of relative risk of cancer incidence associated with diabetes

Legend:

Cancers are ordered (top–bottom) by number of cohorts.

NHL: non–Hodgkin's lymphoma.





Highlights

- Subjects with diabetes have an increased risk of several cancers
- The relative risk of cancer incidence associated with diabetes increased until 2000
- Between 2000 and 2010, the relative risk has been stable
- In contrast, the relative risk of cancer mortality has been constant
- Cancer should be considered amongst the complications of diabetes