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Type 1 diabetes mellitus and risk of cancer: a meta-analysis of observational studies

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Abstract

Objective: Previous observational studies have focused on the link between type 2 diabetes and the risk of cancer. However, the association between type 1 diabetes and the risk of cancer has not been well addressed. This study aimed to investigate the association between type 1 diabetes and the risk of cancer by using a meta-analysis of observational studies.

Methods: We searched PubMed and EMBASE for observational studies that examined the association between type 1 diabetes and cancer in April 2017. We calculated the pooled odds ratios (ORs) or relative risks (RRs) with confidence intervals (CIs) from individual studies based on a random-effects model meta-analysis.

Results: We included a total of 15 observational studies with two case–control studies and 13 cohort studies involving 31 893 cancer patients among a total of 1 915 179 participants in the final analysis. In the random-effects meta-analysis of all studies, patients with type 1 diabetes had an increased risk of cancer (OR or RR, 1.29; 95% CI, 1.09–1.52; $n = 15$; $I^2 = 95.2\%$). In the subgroup meta-analysis by type of cancer, type 1 diabetes significantly increased the risk of cancers of stomach, lung, pancreas, liver, ovary and kidney, whereas it significantly decreased the risk of breast cancer (OR or RR, 0.91; 95% CI, 0.86–0.95; $n = 9$; $I^2 = 0\%$).

Conclusion: This meta-analysis suggests that type 1 diabetes is associated with the increased risk of several types of cancer and the decreased risk of breast cancer. However, the plausible mechanisms for the decreased risk of breast cancer remain unclear. Further prospective studies with proper adjustment for possible confounding factors are warranted.

Key words: type 1 diabetes, cancer, observational study, cohort study, meta-analysis

Introduction

It has been reported that patients with diabetes mellitus have an excess risk of cancer by 20–25% compared to those without diabetes (1). Specifically, there is increasing epidemiological evidence that type 2 diabetes mellitus is associated with an increased risk of certain site-specific cancers, such as breast cancer, colorectal cancer, liver cancer and pancreatic cancer (2). However, the association between type 1 diabetes and cancer remains unclear because relatively a small number of studies have investigated the risk of cancer in patients with type 1 diabetes, and the findings on the association between type 2 diabetes and the risk of cancer could not be directly applied to type 1 diabetes because patients with type 2 diabetes are usually older and more obese than those with type 1 diabetes (3). Although hyperglycemia is common to these two types of diabetes mellitus (DM), insulin resistance and hyperinsulinemia are more noticeable in type 2 diabetes than type 1 diabetes, and type 2 diabetes is less exposed to exogenously administered insulin administration than type 1 diabetes (4). Plausible mechanisms for the increased risk of cancer in patients with type 2 diabetes are hyperglycemia, hyperinsulinemia and insulin resistance (5).

Previous observational epidemiological studies such as case–control studies and cohort studies have reported inconsistent findings on the association between type 1 diabetes and the risk of cancer (3, 4,6–14). Some studies (3,4,6,7,10,13,14) concluded that type 1 diabetes was associated with an increased risk of cancer, whereas others (8,9,11,12) indicated that there was no significant association between them. Iatrogenic insulin excess itself, possible mutagenic effects of insulin or insulin analog, and insulin-like growth factor-1 (IGF-1) due to excess insulin might be the potential biological plausibility for the increase risks of certain cancers (15–17). However, there is no published meta-analysis on this topic until now.

This study aimed to investigate the association between type 1 diabetes and the risk of cancer by using a meta-analysis of observational epidemiological studies according to various factors such as type of cancer, study design, study region, sample size, gender and methodological quality of study.

Methods

Literature search

Studies were identified by searching PubMed and EMBASE in April 2017, using keywords related to the association between type 1 diabetes and the risk of cancer. The followings were keywords for literature search: 'type 1 diabetes' and 'cancer'. We also reviewed the list of references from the identified publications in order to locate studies that might not be found during the search. There was no restriction on the language of publication.

Selection criteria

We included observational studies such as case–control studies and prospective or retrospective cohort studies that investigated the association between type 1 diabetes and the risk of cancer, reporting measures of outcomes with adjusted odds ratios (ORs) or relative risks (RRs) and 95% confidence intervals (CIs). For data that were identical in more than one study or duplicated, the more comprehensive or first published study was included in the analysis.

Selection of relevant studies

Two of the authors (M.F.S., G.J.) independently evaluated the eligibility of all studies extracted from the databases based on the pre-determined

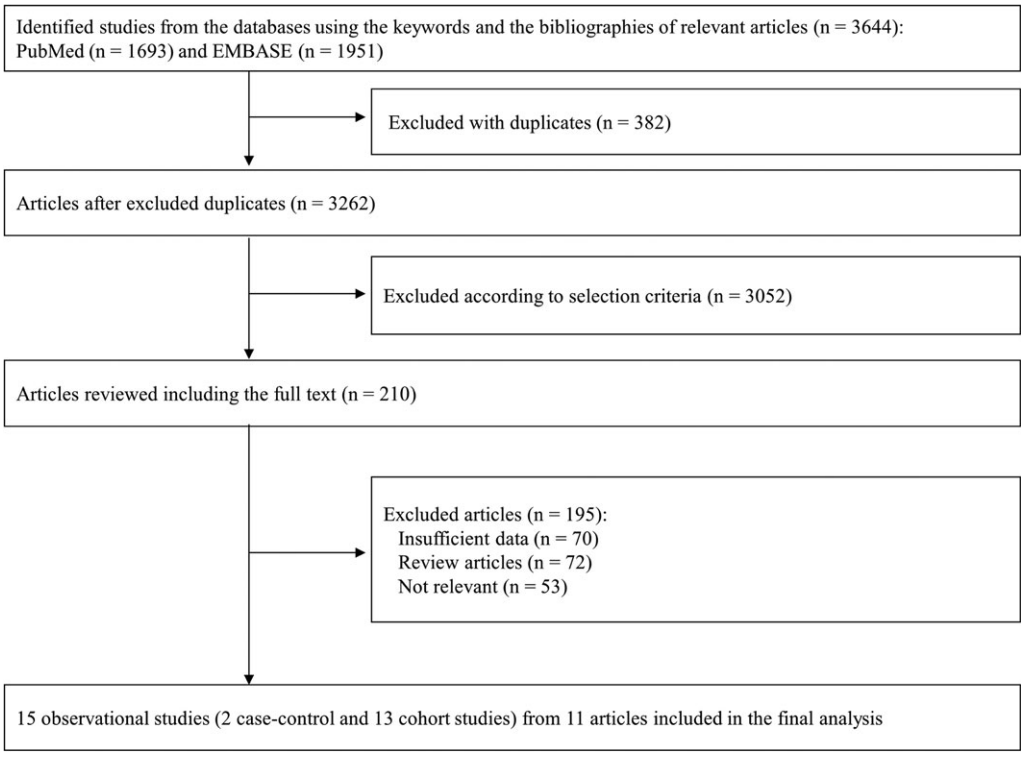

Figure 1. Flow diagram of identification of relevant studies.

Table 1. General characteristics of the studies included in the final analysis ($n = 15$; 11 articles)

Study [Reference No.]	Type of study	Country	Years enrolled	Population and definition of type 1 diabetes mellitus	Type of cancer	OR or RR (95% CI)	Adjusted variables
Hjaldgrim et al. (6)	Retrospective cohort study	Denmark	1973–1992	1659 patients with diabetes mellitus diagnosed before the age of 20 years and 1499 patients with insulin treated diabetes	All types	0.9 (0.6–1.3)	Age, sex and age at onset of diabetes
La vecchia et al. (7)	Case–control	Italy	1984–1996	428 Hepatocellular carcinoma patients (317 males and 111 females) and 1502 controls: subjects with diabetes below age 45 considered as having insulin-dependent diabetes	Primary liver cancer	2.1 (1.0–4.8)	Alcohol, tobacco consumption, history of hepatitis, liver cirrhosis, body mass index and history of cancer in first degree relatives
Hassan et al. (8)	Case–control study	United States	1994–1995	115 Hepatocellular carcinoma patients and 230 non liver cancer patients: insulin-dependent diabetes by confirmation of the diagnosis and the use of insulin treatment from the medical records	Hepatocellular carcinoma	4.40 (1.40–13.6)	Hepatitis virus infection, alcohol consumption and cigarette smoking
Zendehdel et al. (9)	Retrospective cohort study	Sweden	1965–1999	29 187 patients aged 30 years old or younger at first hospitalization for diabetes (14 864 men and 14 323 women)	All types of cancer	1.20 (1.00–1.30)	Age, sex and calendar year at follow-up
Swerdlow et al. (10)	Prospective cohort	United Kingdom	1972–2003	23 834 patients with diabetes diagnosed at ages under 30 years (12 687 men and, 11 047 women)	All types of cancer	0.95 (0.84–1.08)	Age, sex and duration of diabetes
Goossens et al. (11)	Prospective cohort	United Kingdom	1998–2012	329 168 patients with type 1 diabetes formally diagnosed or younger than 30 years and using insulin only at index date or type 2 diabetes formally diagnosed or using anti diabetic drug and 307 315 controls	Bladder cancer	0.77 (0.57–1.05)	Age, sex, smoking status and body mass index
Harding et al. (4)	Prospective cohort study	Australia	1997–2008	80 676 patients with type 1 diabetes classified as type 1 on the National Diabetes Service Scheme and diagnosed before the age of 30 years (42 032 men and 38 644 women)	All types of cancer	1.06 (1.02–1.10)	Sex, single calendar year and 5-year age-group
Hsu et al. (3)	Retrospective cohort study	Taiwan	2000–2008	14 619 patients with type 1 diabetes with the ICD-9-CM codes 250.00 or 250.03 (6 867 men and 7 752 women)	All types of cancer	1.13 (1.05–1.22)	Age, sex and calendar year
Valent et al. (12)	Prospective cohort	Italy	2002–2014	6728 patients with diabetes whose only medication prescribed since inclusion in the registry was insulin and 1 080 260 non-diabetic subjects	Digestive organs	2.68 (2.34–3.10)	Age, sex and diabetic status
Carstensen et al. (13)	Pooled analysis of five cohort studies	Australia, Denmark, Finland, Scotland, and Sweden	1972–2012	People with diabetes diagnosed below the age of 40 years in 3.9 million person-years (men in 1.975 million person-years and women in 1.958 million person-years)	All types of cancer	1.04 (0.98–1.10)	Sex, age and calendar time
Hemminki et al. (14)	Retrospective cohort study	Sweden	1997–2010	32 635 patients with diabetes before the age of 30 years during the period 1964 to 1996 and insulin-dependent diabetes with the ICD code E10 (17 986 men and 14 649 women)	All types of cancer	2.91 (1.96–4.15)	Age, sex, period of diagnosis, socioeconomic status, and region

ICD-9-CM, International Classification of Disease ninth Version – Clinical Modification; OR, odds ratio; RR, relative risk; CI, confidence interval.

Table 2. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa Scale

Case–control study ($n = 2$)	Selection				Comparability	Exposure			Total
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Nonresponse rate	
La vecchia et al. (7)	1	1	1	1	1	1	1	1	8
Hassan et al. (8)	1	1	1	1	2	1	1	0	8

Cohort study ($n = 9$)	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Hjaldgrim et al. (6)	1	0	1	1	1	1	1	1	7
Zendehdel et al. (9)	1	0	1	1	2	1	1	0	7
Swerdlow et al. (10)	1	1	1	0	2	1	1	0	7
Goossens et al. (11)	1	1	1	1	1	1	1	1	8
Harding et al. (4)	1	1	1	0	2	1	1	0	7
Hsu et al. (3)	1	1	1	1	2	1	1	0	8
Valent et al. (12)	1	0	1	1	1	1	1	1	7
Carstensen et al. (13)	1	1	1	1	2	1	1	0	8
Hemminki et al. (14)	1	1	1	1	1	1	1	1	8

selection criteria. The two evaluators solved their disagreements on selection by discussion. The following data were obtained from the studies included in the final analysis: study name (year of publication and the family name of the first author), type of study design, country, years enrolled, population (gender), type of cancer, OR or RR with 95% CI, and adjusted variables.

Assessment of methodological quality

The methodological quality of the included studies in the final analysis was assessed based on the Newcastle-Ottawa Scale (NOS) for assessing the quality of case–control studies and cohort studies in meta-analyses (18). The score of the NOS system ranges between 0 and 9 and consists of three subscales: selection of studies, comparability and exposure. In the current study, we considered a study awarded a score of more than a mean of all studies as having high quality due to the absence of the established criteria for the high- or low-quality of a study.

Main and subgroup analyses

In the main analysis, we evaluated the association between type 1 diabetes and the incidence of cancer. Also, we performed subgroup meta-analyses by type of cancer, gender, region of study population (America, Europe and Asia), sample size and methodological quality of studies.

Statistical analyses

We used adjusted ORs or RRs and 95% CIs reported in individual articles to calculate a pooled OR or RR with 95% CI. Heterogeneity in results across studies was evaluated using Higgins I^2, which measures the percentage of total differences across studies (19). We calculated I^2 as follows:

$$I^2 = 100\% \times (Q - \mathrm{df})/Q,$$

where Q represents Cochran's heterogeneity statistic, while df is the degrees of freedom. Negative values of I^2 are set at zero; I^2 lies between 0% (heterogeneity not observed) and 100% (heterogeneity at its maximum). A value of I^2 greater than 50% indicated substantial heterogeneity.

We used a random-effects model meta-analysis based on the DerSimonian and Laird method because most cohort studies were conducted in the different populations (20). Also, we used Begg's funnel plot and Egger's test to examine publication bias regarding the studies included in the final analysis. An asymmetrical Begg's funnel plot or a P value of less than 0.05 by Egger's test denotes the existence of publication bias. Stata SE version 12.1 software package (StataCorp, College Station, TX, USA) was used for statistical analysis.

Results

Identification of relevant studies

Figure 1 displays a flow diagram which demonstrates how relevant studies were identified. We identified a total of 3644 articles by searching PubMed and EMBASE. A total of 382 duplicated articles and additional 3052 articles that did not meet the selection criteria were excluded in the first selection. In the final selection, we reviewed the full texts of the remaining 210 articles, and additional 195 articles were excluded because of various reasons, which are

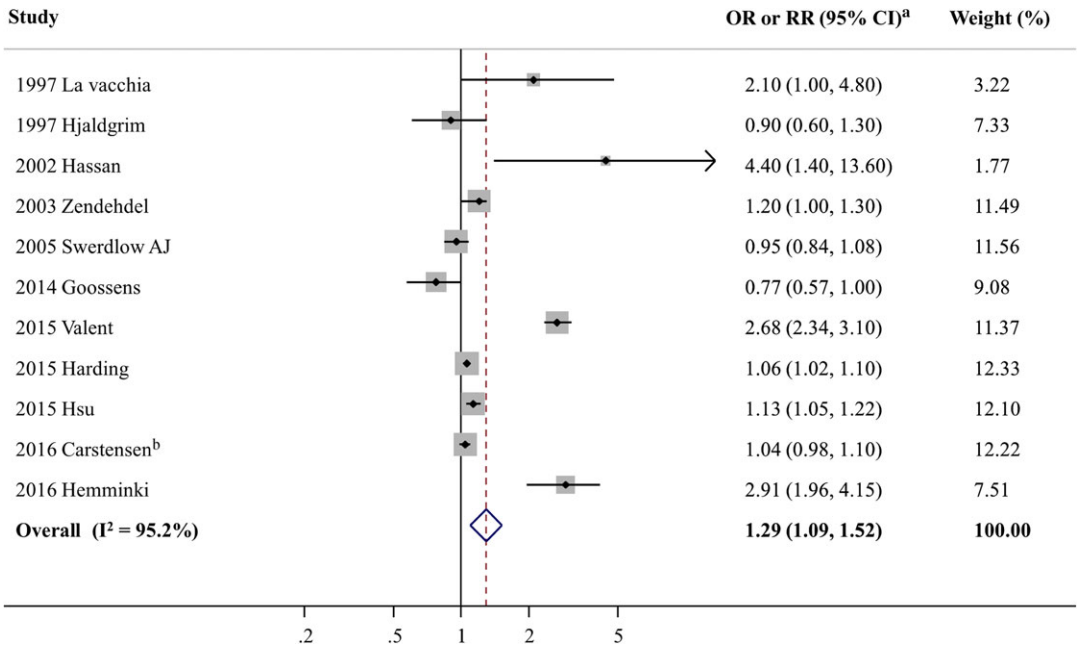

Figure 2. Association between type 1 diabetes mellitus and the risk of cancer in a random-effects model meta-analysis of observational studies (n = 15; 11 articles). [a]Random-Effects Model. OR, odd ratio; RR, relative risk; CI, confidence interval. [b]A pooled study of five cohort studies.

indicated in Figure 1. A total of 11 articles (3,4,6–14) were included in the final analysis.

General characteristics of studies

We included a total of 15 observational studies with two case–control studies and 13 cohort studies from 11 articles, which involved 31 893 cancer patients among a total of 1 915 179 participants in the final analysis. The general characteristics of the included studies are shown in Table 1. The studies were carried out in the following countries: Sweden (n = 3), Australia (n = 2), UK (n = 2), Denmark (n = 2), Italy (n = 2), Finland (n = 1), Scotland (n = 1), US (n = 1) and Taiwan (n = 1). The average age was 29.6 years and ranged between 17 and 59 years. The enrollment periods for participants across the studies ranged between 1965 and 2014, and the periods of follow-up in cohort studies ranged between 8 and 20 years.

Methodological quality of studies

The methodological quality of studies based on the NOS is shown in Table 2. The quality scores ranged between 7 and 8 with an average score of 7.4 for cohort studies and 8 for a case–control study. Four cohort studies were considered as having high quality with a score of 8.

Main analysis on type 1 diabetes and risk of cancer

As shown in Figure 2, a random-effects meta-analysis of all 15 studies showed a significant positive association between type 1 diabetes and the risk of cancer (OR or RR, 1.29; 95% CI, 1.09–1.52; I^2 = 95.2%).

Subgroup meta-analyses

Table 3 summarizes the results from the subgroup meta-analyses by various factors. In the subgroup meta-analysis by type of cancer, type 1 diabetes was associated with an increased risk of thyroid cancer (RR, 1.40; 95% CI, 1.19–1.66; I^2 = 0.00%; n = 6), lung cancer (RR, 1.09; 95% CI, 1.02–1.17; I^2 = 25.6%; n = 8), esophagus (RR, 1.06; 95% CI, 1.02–2.42; I^2 = 16.7%; n = 6), stomach cancer (RR, 1.44; 95% CI, 1.29–1.61; I^2 = 0.00%; n = 9), pancreatic cancer (RR, 1.34; 95% CI, 1.18–1.52; I^2 = 93.3%; n = 9), liver cancer (RR, 2.35; 95% CI, 2.12–2.61; I^2 = 96.6%; n = 9), ovarian cancer (RR, 1.17; 95% CI, 1.04–1.32; I^2 = 69%; n = 7), endometrial cancer (RR, 1.67; 95% CI, 1.22–2.30; I^2 = 40.5%; n = 8), and kidney cancer (RR, 1.37; 95% CI, 1.23–1.52; I^2 = 22.9%; n = 8).

On the contrary, type 1 diabetes reduced a risk of breast cancer (RR, 0.91; 95% CI, 0.86–0.95; I^2 = 0.0%; n = 9). There was no significant association between type 1 diabetes and the risk of cancers of brain/nervous system, buccal cavity, colorectum, cervix uteri, bladder, testis, lymphoma, leukemia, multiple myeloma, bone, connective tissue and skin.

The remaining subgroup meta-analyses by region, sample size, sex and study quality also showed a positive association between type 1 diabetes and the risk of cancer.

Assessment of publication bias

No publication bias was found in the included studies with an asymmetrical Begg's funnel plot and Egger's test (P for bias = 0.218; Figure 3).

Discussion

This meta-analysis of observational epidemiological studies including case–control studies and cohort studies found that type 1 diabetes was significantly associated with an increased risk of cancers such as stomach cancer, lung cancer, pancreatic cancer, liver cancer, ovarian cancer and kidney cancer. Conversely, type 1 diabetes was significantly associated with a decreased risk of breast cancer.

There are some biological mechanisms that might explain a positive association between type 1 diabetes and the risk of cancer as shown in our meta-analysis. The relationship between type 1 diabetes and cancer could either be a marker of certain underlying biologic factors such as

Table 3. Association between type 1 diabetes mellitus and the risk of cancer in subgroup meta-analyses by various factors[a]

Factors	No. of study[b]	Summary OR or RR (95% CI)	Heterogeneity, I^2 (%)
All [3,4,6–14]*	15	1.29 (1.09–1.52)	95.2
Type of cancer			
Brain and/or nervous system [9,10,13]	7	0.96 (0.88–1.06)	0.0
Thyroid [9,13]*	6	1.40 (1.19–1.66)	0.0
Lung cancer [3,9,10,13]*	8	1.09 (1.02–1.17)	25.6
Buccal cavity [9,14]	2	1.79 (0.96–3.36)	0.0
Esophagus [12,13]	6	1.60 (1.06–2.42)	16.7
Stomach cancer [3,9,10,12,13]*	9	1.44 (1.29–1.61)	0.00
Colorectal cancer [9,10]	2	0.90 (0.61–1.31)	20.9
Pancreatic cancer [3,9,10,12,13]	9	1.34 (1.18–1.52)	94.4
Liver [3,8,9,12,14]*	9	2.35 (2.12–2.61)	96.6
Breast cancer [3,6,9,10,13]*	9	0.91 (0.86–0.95)	0.0
Cervix uteri [3,9,10,13]	8	1.24 (0.99–1.56)	49.4
Ovary [9,10,13]*	7	1.17 (1.04–1.32)	69
Endometrium [3,9,10,13]*	8	1.67 (1.22–2.30)	40.5
Bladder [3,9,10,13]	8	0.98 (0.88–1.09)	0.0
Kidney [3,9,10,13]*	8	1.37 (1.23–1.52)	22.9
Prostate [3,10,13]	7	1.15 (0.30–4.41)	98.8
Testis [10,13]	6	0.88 (0.76–1.02)	0.0
Lymphoma [9,10,13,14]	8	1.02 (0.85–1.23)	0.0
Leukemia [9,10,13]	7	1.01 (0.88–1.16)	0.0
Multiple myeloma [13]	5	0.90 (0.71–1.15)	12.6
Bone [9]	1	1.00 (0.20–3.00)	n.a.
Connective tissue [9]	1	1.10 (0.40–2.60)	n.a.
Skin, melanoma [9,10,13]	7	0.89 (0.77–1.02)	3.5
Skin cancer, non-melanoma [9,14]	2	1.15 (0.60–2.20)	16.9
Region			
Europe [6,7,9,10,11,12,13,14]	12	1.17 (1.12–1.23)	96.4
America [8]*	1	4.40 (1.41–13.71)	n.a.
Asia [3]*	1	1.13 (1.05–1.22)	n.a.
Australia [4]	1	1.02 (0.96–1.08)	n.a.
Sample size			
≥20.000 participants [4,9–14]*	11	1.11 (1.07–1.14)	97.0
<20.000 participants [3,6–8]	4	1.13 (1.05–1.22)	67.5
Sex			
Male [3,4,7,13]*	8	1.12 (1.09–1.15)	85.8
Female [3,4,7,13]*	8	1.14 (1.11–1.16)	75.6
Study quality (cohort studies)			
Low [4,6,9,10,12]	5	1.12 (1.08–1.16)	97.6
High [3,11,13,14]*	8	1.08 (1.03–1.13)	91.5

[a]All the subgroup meta-analyses were performed based on a random-effects model.
[b]Carstensen et al.'s study (Reference No.9) consists of five cohort studies.
*Statistically significant; n.a., not applicable.
OR, odds ratio; RR, relative risk; CI, confidence interval.

insulin resistance that alter the risk of cancer or be linked directly to hyperglycemia (2,21,22). Also, patients with type 1 diabetes are usually characterized by pancreatic β-cell autoimmunity with insulin deficiency that generally necessitates the lifelong provision of exogenous insulin, which is directly absorbed into systemic circulation. Supraphysiologic concentrations of insulin are required for systemic circulation, to enable sufficient levels of insulin in portal circulation to restrain hepatic gluconeogenesis (23). The iatrogenic insulin excess and possible mutagenic effects of insulin or insulin analog might be responsible for some increased cancer risks (15,16).

The increased risk of stomach cancer in patients with type 1 diabetes could be explained by several possible mechanisms. First, both the increase in body weight and the abdominal fat deposit have been blamed on the long-term use of insulin to treat diabetic patients (24). A meta-analysis of cohort studies indicated that overall, excess body weight was associated with an increased risk of stomach cancer (25). Also, the increased risk of stomach cancer among patients with type 1 diabetes might be linked to a high prevalence of helicobacter pylori infection in those patients or a high incidence of pernicious anemia that is closely related to a high risk of stomach cancer because parietal cell antibodies are more frequent in patients with type 1 diabetes, compared to the general population (26,27).

It was already reported that diabetes was significantly associated with an increased risk of lung cancer, especially in women from the meta-analysis of 34 observational studies although it did not differentiate type 1 diabetes from type 2 diabetes (28). Potential mechanisms includes increased levels of insulin-like growth factor-1 (IGF-1) due to excess insulin, which play an important role in lung carcinogenesis (17) and hyperglycemia leading to the damage to the lung structure such as emphysema, which is an independent risk factor for lung cancer (29,30).

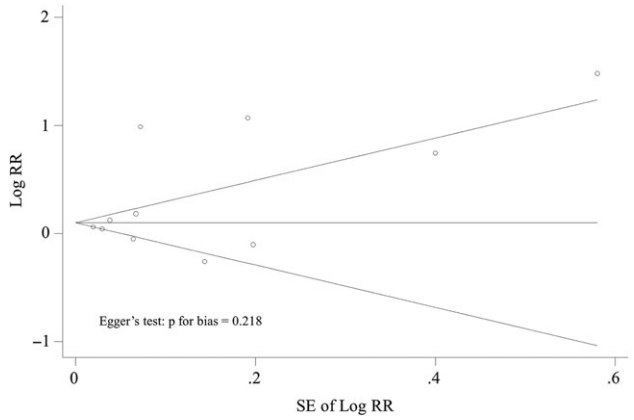

Figure 3. Begg's funnel plots and Egger's test for identifying publication bias in the meta-analysis of observational studies. OR, odd ratio; RR, relative risk; SE, standard error.

Although the causal mechanisms for the increased risk of liver cancer in type 1 diabetes remain unclear, possible biological mechanisms are a result of alteration in hepatocellular activity, possibly mitosis related to metabolic changes in patients with diabetes (31) and steatohepatitis related to obesity and fibrotic progression to cirrhosis resulting in liver cancer (32).

It has been proposed that hyperinsulinemia and raised androgen levels found in menstruating women with type 1 diabetes are associated with an increased risk of ovarian cancer (10). However, the exact mechanisms remain unclear because the levels of insulin and androgen are also raised in women with type 2 diabetes. Also, excess insulin could directly stimulate the growth of endometrial cells and increase the levels of estrogen resulting in proliferation of endometrial cells, both of which consequently could increase the risk of endometrial cancer (33). Like other cancers, increased insulin resistance, excess insulin and obesity might be possible mechanisms for the increased risk of kidney cancer in patients with type 1 diabetes (34).

The interesting finding in our study is that type 1 diabetes was associated with a decreased risk of breast cancer by 9%. This is contrary to the findings that the risk of breast cancer in women with type 2 diabetes was increased by 20–27% from the previous meta-analyses (35,36). Among the eight studies on breast cancer, only a pooled analysis of five studies (13) indicated a significant decreased risk of breast cancer in patients with type 1 diabetes, whereas three studies (3,9,10) reported no significant association. Although Carstensen et al. of the pooled study (13) mentioned that their contradictory finding might be confounded by other breast cancer risk factors such as parity, the plausible mechanisms or reasons for their findings remain unclear. Further prospective studies with proper adjustment for possible confounding factors are warranted to confirm this finding.

Recent meta-analyses reported mainly the association between type 2 diabetes or overall diabetes and the risk of individual cancers (28,37–39). To the best of our knowledge, this study is considered to be the first meta-analysis of observational epidemiological studies that investigated the association between type 1 diabetes and the risk of cancer. We found a modest increase, 29% in the risk of overall cancers in patients with type 1 diabetes compared to those without type 1 diabetes. However, those risks were much higher in several types of cancer, i.e. by 40% for thyroid cancer, 44% for stomach cancer, 34% for pancreatic cancer, 135% for liver cancer, 67% for endometrial cancer and 37% for kidney cancer (Table 3). Also, we found that type 1 diabetes was associated with a slightly reduced risk of breast cancer by 9%.

Our study has limitations. First, there is a possibility of misclassification of type 2 diabetes into type 1 diabetes, which might lead to an overestimation of the association between type 1 diabetes and the risk of cancer. Also, the criteria for the definition of type 1 diabetes varied across the included studies. Hassan et al.'s study just mentioned insulin-dependent DM or non-insulin-dependent DM in the results section without mentioning how they defined them (8), while Valent et al. defined it as insulin treated diabetes (12). Also, Hsu et al.'s study used the International Classification of Disease ninth version, Clinical Modification (ICD-9-CM) codes for defining type 1 diabetes (3). The remaining studies defined patients with type 1 diabetes as those who were 30 years old or younger, or diabetes diagnosed before the age of 30 or 45 years (4,6,7,9–11,14). When we performed a subgroup meta-analysis excluding three studies (1997 Hjaldgrim; 2002 Hassan; 2015 Valent), which used only insulin treatment as the criteria for type 1 diabetes (data not shown in figure or table), the increased risk of cancer became smaller than that of the previous analysis (RR, 1.10; 95% CI, 1.00–1.21). Last, there might exist confounders on the association between type 1 diabetes and the risk of cancer because most of the included studies did not adjust important risk factors such as tobacco consumption, alcohol intake, obesity, physical activity, family history of cancer and socioeconomic status for the development of cancer.

Conclusions

We found that type 1 diabetes was associated with an increased risk of overall cancers by using a meta-analysis of observational studies and a decreased risk of breast cancer. However, further studies are warranted to confirm our findings because of the possibility of misclassification and the existence of potential confounders on the association them.

Type of study design

Systematic Review and Meta-Analysis

Group name

The Korean Meta-Analysis (KORMA) Study Group

Funding

None.

Conflict of interest statement

We declare no competing interests.

Contributors

Mukete F. Sona: conception, design, evaluation of the eligibility of studies, acquisition of data, statistical analysis and manuscript writing. Seung-Kwon Myung: conception, design, statistical analysis, manuscript writing, critical review, interpretation of data, editing and final approval of the version to be published. Keeho Park:

critical review and interpretation of data. Galsuren Jargalsaikhan: evaluation of the eligibility of studies and acquisition of data.

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