Cancer Risk Associated with Use of Metformin and Sulfonylurea in Type 2 Diabetes: A Meta-Analysis

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ABSTRACT

Objective. Oral antidiabetic drugs (including metformin and sulfonylurea) may play a role in the relationship between type 2 diabetes and cancer. To quantify the association between metformin and sulfonylurea and the risk of cancer, we performed a meta-analysis of available studies on the issue.

Materials and Methods. We performed a MEDLINE search for observational studies that investigated the risk of all cancers and specific cancer sites in relation to use of metformin and/or sulfonylurea among patients with type 2 diabetes mellitus. Fixed- and random-effect models were fitted to estimate the summary relative risk (RR). Between-study heterogeneity was tested using χ^2 statistics and measured with the I^2 statistic. Publication bias was evaluated using funnel plot and Egger’s regression asymmetry test.

Results. Seventeen studies satisfying inclusion criteria

and including 37,632 cancers were evaluated after reviewing 401 citations. Use of metformin was associated with significantly decreased RR of all cancers (summary RR 0.61, 95% confidence interval [CI] 0.54–0.70), colorectal cancer (0.64, 95% CI 0.54–0.76), and pancreatic cancer (0.38, 95% CI 0.14–0.91). With the exception of colorectal cancer, significant between-study heterogeneity was observed. Evidence of publication bias for metformin-cancer association was also observed. There was no evidence that metformin affects the risk of breast and prostate cancers, nor that sulfonylurea affects the risk of cancer at any site.

Conclusions. Metformin, but not sulfonylurea, appears to reduce subsequent cancer risk. This has relevant implications in light of the exploding global epidemic of diabetes. *The Oncologist* 2012;17:813–822

INTRODUCTION

Type 2 diabetes is a condition affecting a substantial and increasing proportion of the population worldwide [1]. Much evidence has been accumulating to suggest that diabetes is associated with an increased risk of cancer [2]. The mecha-

nisms are yet to be investigated, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis [3–5], although hyperglycemia itself seems to promote carcinogenesis [6].

Different mechanisms, activated by endogenous hyperin-

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sulinemia or exogenous insulin, can promote cancer progression. First, insulin resistance may favor the availability of insulin-like growth factor (IGF-I), overactivating the IGF-I receptors, which may contribute to the cancerogenesis and cancer promotion in hyperinsulinemic patients [7]. Second, IGF-I might increase the risk of cancer through its anti-apoptotic activity [8]. Finally, insulin activity may affect the mitogenic pathways that include an overactivation of the mammalian target of rapamycin (mTOR) enzyme [9].

Consequently, the treatments that may cause hyperinsulinemia, such as sulfonylurea and exogenous insulin, are thought to increase the risk of cancer [10, 11]. Conversely, treatments that decrease insulin resistance, such as metformin, which act as growth inhibitors for epithelial cells by reducing mTOR activity, are thought to reduce the risk of cancer development [12–15].

The results from epidemiologic studies have been inconsistent, however, and the reasons underlying this heterogeneity, including differences between cancer sites, study populations, and design, need to be further investigated. In light of the increasing prevalence of patients under treatment with oral anti-diabetic drugs, efforts aimed at elucidating the association between use of these drugs and cancer risk have major implications for public health. With these premises, we performed a systematic review and meta-analysis of available studies to better define and quantify the effect of metformin and sulfonylurea on risk of cancer overall, as well as of different cancer sites, in patients with type 2 diabetes.

MATERIALS AND METHODS

Search Strategy and Study Selection

We carried out a MEDLINE search of the literature to identify observational studies published up to May 2011 that investigated the association between metformin or sulfonylurea and cancer. The following keywords and/or corresponding MeSH terms were used: “diabetes mellitus, type 2” AND (“metformin” OR “sulfonylurea” OR “biguanides” OR “hypoglycemic agents”) AND (“neoplasms” OR “cancer”). In addition, the reference lists of reviews and meta-analyses published on this issue were hand-checked to identify additional relevant publications [2, 3, 16–18].

Inclusion and Exclusion Criteria

The search was restricted to observational studies due to the absence of meaningful data from randomized clinical trials. Studies were included if based on cohort or case-control design provided that they (a) specifically mentioned that participants were affected by type 2 diabetes mellitus; (b) investigated exposure to metformin and/or sulfonylurea; (c) assessed either the risk of all cancers (main outcome) or the risk of cancer at specific sites (secondary outcome), with the exclusion of studies including prevalent or recurrent cases of cancer; and (d) reported crude or adjusted estimates of the association between exposure and outcome (that is, relative risk [RR], odds ratio, hazard or rate ratio, and the corresponding 95% confidence interval [CI] or *p*-value), or sufficient raw data to allow their cal-

culation. When data were published more than once, the most recent and complete publication was considered. Two readers (D.S. and L.S.) independently determined the eligibility of each article for inclusion. Discrepancies between readers were resolved in conference.

Data Collection

For each included study, we extracted details on study design, country, publication year, exposure and reference therapy (e.g., no use of metformin and no use of sulfonylurea, insulin, metformin, or sulfonylurea), cancer site, adjustment and stratification variables, number of cancer cases, exposure definition (monotherapy or use of more than one therapy), RR (or other association measures), and the corresponding 95% CI.

Statistical Methods

The summary RR for exposure to metformin or sulfonylurea was the measure of interest. Analyses were performed for specific reference therapies and cancer sites on condition that the corresponding estimates were reported by at least three studies. Whenever possible, we pooled adjusted estimates from the original studies; otherwise we used raw data and computed unadjusted RRs. We pooled the original estimates by using both the fixed-effects model and the random-effects model proposed by DerSimonian and Laird [19]. Under the fixed-effects model, it is assumed that there is one true effect size that is shared by all the included studies. It follows that the combined effect is the estimate of this common effect size. Conversely, in the random-effects model, the true effect could vary from study to study; thus, the study-specific estimates are assumed to be a random sample of the relevant distribution of effects, and the combined effect estimates the mean effect in this distribution. In this case, it is important to evaluate between-study variability and incorporate it in the summary-estimate calculation to provide a more accurate measure of the summary-estimate variability. Heterogeneity between study-specific estimates was tested using the *Q* statistic, which is computed by summing the weighted squared deviations of each study estimate from the fixed-effects summary estimate [20]. When a significant heterogeneity was found, the results from the random-effects model were presented. Moreover, the total variation across studies that is due to heterogeneity rather than chance was evaluated using the *I*² statistic [21].

Between-study sources of heterogeneity were investigated by stratifying original estimates according to some study characteristics potentially relevant in causing heterogeneity, i.e., study design (cohort or case-control), geographic area (Europe, Asia, or North America), control for possible confounders (adjusted or unadjusted estimates), exposure definition (monotherapy versus use of more than one therapy), and reference therapy (any or specific other antidiabetic agent). In the presence of a significant summary RR, an influence analysis was conducted by omitting one study at a time, to identify to what extent the results were influenced by a single study. Finally, publication bias was evaluated through funnel plot analysis and the Egger's test [22].

For all hypothesis tests, evidence was based on *p* < .05,

Figure 1. Flow chart of the selection of studies for inclusion in the meta-analysis.

and the 95% CIs were therefore presented. The corresponding calculations and graphical visualizations of forest and funnel plots were respectively carried out using RevMan version 5.1 (Nordic Cochrane Center) and STATA Software Program version 9 (STATA, College Station, TX).

RESULTS

Figure 1 shows the flow diagram for the study inclusion. On the basis of title and abstract, we identified 401 papers. We excluded 241 of them because they were not related to the study objective. The remaining 160 articles were considered of interest, and their full text was retrieved for detailed evaluation. Of these, 143 articles were further excluded because they did not satisfy the inclusion criteria. The remaining 17 studies [23–39] complied with the inclusion criteria and were considered for meta-analysis. The main characteristics of the studies included are reported in Table 1. They investigated the risk of cancer associated with use of both metformin and sulphonylurea (11 studies) or metformin alone (6 studies). They were based on 37,632 cancers at any site (3,931 cases, 7 studies), colon and rectum (972 cases, 5 studies), prostate (26,234 cases, 4 studies), pancreas (1,192 cases, 4 studies), breast (1,068 cases, 4 studies), or other specified sites (1,474 cases, 5 studies).

Figure 2 shows the study-specific and summary RRs of cancer associated with metformin. The summary RRs and the corresponding 95% CIs were, respectively, 0.60 (95% CI, 0.50–0.73), 0.65 (95% CI, 0.50–0.83), and 0.56 (95% CI, 0.40–0.78) when the reference therapy was no use of metformin, sulphonylurea, and insulin. When all reference therapies taken together, the summary RR was 0.61 (95% CI, 0.54–0.70). In both cohort and case-control studies, a significant difference in the summary estimates was detected. However, no significant difference was found between summary estimates considering all reference categories together ($p = .49$). Moreover, a high between-study heterogeneity was found; in fact, the I^2 statistic was 85% for metformin versus no use of metformin, 81% for metformin versus sulphonylurea, 86% for metformin versus insulin, and 84% for metformin versus all reference therapies. Among the sources of heterogeneity, the

adjustment of original estimates significantly modified the investigated effect: RRs of 0.60 (0.55–0.73) and 0.34 (0.24–0.49) were observed, respectively, for adjusted and unadjusted estimates ($p = .004$).

The association between use of metformin and specific cancer sites is shown in Figure 3. A significant reduction of colorectal cancer risk was observed (summary RR, 0.64; 95% CI, 0.54–0.76), without any evidence of between-study heterogeneity ($p = .291$ and $I^2 = 19\%$). Also for pancreatic cancer there was evidence of significant risk reduction (summary RR, 0.38; 95% CI, 0.14–0.91), but significant between-study heterogeneity was noted ($p < .001$ and $I^2 = 89\%$). No differences were found between the summary estimate calculated using different exposure definition (monotherapy versus use of more than one therapy) for metformin ($p = .33$). Influence analysis showed that heterogeneity was in large part due to one study [24]; when omitting it, the I^2 dropped to 28% and the summary RR dropped to 0.27 (95% CI, 0.18–0.40). There was no evidence that use of metformin is associated with the risk of breast and prostate cancers, with the summary RRs being 0.87 (95% CI, 0.69–1.10) and 0.92 (95% CI, 0.73–1.17), respectively. Significant between-study heterogeneity was noted for these two cancer sites, and the I^2 statistics were 56% and 78%, respectively, for breast and prostate cancer.

Figure 4 shows study-specific and summary RRs of cancer associated with use of sulphonylurea versus no use of sulphonylurea or insulin taken together stratified for study design. The summary RR was 0.97 (95% CI, 0.82–1.14) overall, 1.02 (95% CI, 0.90–1.17) for cohort studies, and 1.00 (95% CI, 0.76–1.33) for case-control studies. As for metformin, no differences between estimates were highlighted ($p = .89$). Significant between-study heterogeneity was noted with an I^2 statistic of 72%. However, none of the investigated sources of heterogeneity showed evidence of modifying the pooled estimate. The evaluation of the difference between the summary estimates calculated using different exposure definition was not possible for sulphonylurea because only one study reported the use of this drug as monotherapy [24]. The summary associations for use of metformin and the risk of other cancer sites,

Table 1. Chronological summary of literature on oral antidiabetic medications (metformin and sulfonylurea) and cancer risk, and their main characteristics

First author, publication year, country	Study design	Gender	Cancer site	No. cases	Investigated therapy	Reference therapy	Reported RR (95% CI)	Controlled variables/notes
Yang, 2004, U.K. [23]	Case control	MW	Colon and rectum	125	Metformin Sulfonylurea	No metformin No sulfonylurea	1.00 (0.60–1.70) 0.80 (0.50–1.20)	Age, gender, smoking, BMI, diabetes duration, history of cholecystectomy, use of NSAID and/or aspirin
Oliveria, 2007, U.S. [24]	Cohort	MW	Colon and rectum	383	Metformin ^a Sulfonylurea ^a	No metformin No sulfonylurea	0.67 (0.52–0.85) 0.95 (0.76–1.17)	Age, gender, history of polyps, ulcerative colitis, Crohn's disease
			Bladder	178	Metformin ^a Sulfonylurea ^a	No metformin No sulfonylurea	0.99 (0.70–1.39) 0.64 (0.47–1.90)	Age, gender, schistosomiasis, pelvic radiation
			Liver	39	Metformin ^a Sulfonylurea ^a	No metformin No sulfonylurea	0.73 (0.34–1.56) 1.17 (0.60–2.29)	Age, gender, hepatitis B/C, liver cirrhosis, alcoholism
			Pancreas	102	Metformin ^a Sulfonylurea ^a	No metformin No sulfonylurea	1.26 (0.80–1.99) 1.34 (0.87–2.06)	Age, gender, gastrectomy, chronic pancreatitis, deep venous thrombosis, dermatomyositis/polymyositis, alcoholism, hepatitis B/C, history of polyps
Murtola, 2008, Finland [25]	Case control	M	Prostate	24,723	Metformin Sulfonylurea	No metformin No sulfonylurea	0.80 (0.73–0.88) 0.82 (0.77–0.88)	Age, residence, other medications (aspirin, cholesterol-lowering and antihypertensive agents)
Currie, 2009, U.K. [26]	Cohort	MW	Any site	2,051	Metformin ^a	Sulfonylurea Insulin	0.74 (0.65–0.84) 0.70 (0.63–0.79)	Age, gender, smoking
			Colon and rectum	292	Metformin ^a	Sulfonylurea Insulin	0.56 (0.40–0.78) 0.59 (0.43–0.81)	
			Pancreas	89	Metformin ^a	Sulfonylurea Insulin	0.20 (0.11–0.36) 0.22 (0.12–0.38)	
		M	Prostate	301	Metformin ^a	Sulfonylurea Insulin	0.93 (0.67–1.32) 0.91 (0.66–1.27)	
		W	Breast	305	Metformin ^a	Sulfonylurea Insulin	1.02 (0.71–1.45) 0.93 (0.69–1.27)	
Li, 2009, U.S. [27]	Case control	MW	Pancreas	973	Metformin Sulfonylurea	No metformin No sulfonylurea	0.38 (0.22–0.69) 2.52 (1.32–4.84)	Age, gender, ethnic group, smoking, alcohol, family history, BMI, diabetes duration, use of insulin
Libby, 2009, U.K. [28]	Cohort	MW	Any site	771	Metformin	No metformin	0.63 (0.53–0.75)	Age, gender, smoking, BMI, use of insulin and sulfonylurea
			Colon and rectum	116			0.60 (0.38–0.94)	
			Lung	93			0.70 (0.43–1.15)	
		W	Breast	65			0.60 (0.32–1.10)	
		MW	Any site	771	Sulfonylurea	No sulfonylurea	1.12 (0.87–1.47)	Age, gender, smoking, BMI, use of insulin
Bodmer, 2010, U.K. [29]	Case control	W	Breast	305	Metformin	No metformin	1.20 (0.82–1.78)	Age, gender, general practice, BMI, smoking, diabetes duration, use of prandial glucose regulator, A1C, acarbose, estrogens
							1.09 (0.76–1.55)	
							0.44 (0.24–0.82)	
					Sulfonylurea	No sulfonylurea	0.85 (0.58–1.24) 0.79 (0.55–1.15) 1.03 (0.62–1.69)	
Bowker, 2010, Canada [30]	Cohort	MW	Any site	407	Metformin	Sulfonylurea	0.80 (0.65–0.98)	Age, gender, chronic disease score
Donadon, 2010, Italy [31]	Case control	MW	Liver	610	Metformin	Sulfonylurea Insulin	0.39 (0.22–0.73) 0.21 (0.11–0.42)	
					Sulfonylurea	Insulin	0.54 (0.35–0.86)	
Hassan, 2010, U.S. [32]	Case control	MW	Liver	420	Metformin Sulfonylurea	No metformin No sulfonylurea	0.30 (0.20–0.60) 7.10 (2.90–16.90)	Age, gender, ethnic group, education, family history, smoking, alcohol, hepatitis B/C
Landman, 2010, Netherlands [33]	Cohort	MW	Any site	122	Metformin	No metformin	0.46 (0.26–0.83)	Age, gender, diabetes duration, smoking, BMI, systolic blood pressure, A1C, estimated glomerular filtration rate, cholesterol, albumin-to-creatinine ratio, macrovascular complications, use of insulin and sulfonylurea, dietetic therapy
					Sulfonylurea	No sulfonylurea	0.69 (0.36–1.34)	

(continued)

Table 1. (Continued)

First author, publication year, country	Study design	Gender	Cancer site	No. cases	Investigated therapy	Reference therapy	Reported RR (95% CI)	Controlled variables/notes
Azoulay, 2011, U.K. [34]	Case control	M	Prostate	739	Metformin	No metformin	1.23 (0.99–1.52)	Age, alcohol, smoking, obesity, lower urinary tract symptoms, previous cancer, A1C, use of NSAIDs, antihypertensive, statin and other antidiabetic agents
Bosco, 2011, Denmark [35]	Case control	W	Breast	393	Metformin	No metformin	0.81 (0.63–0.96)	Age, complications due to diabetes, obesity, post-menopausal hormone use, parity and use of hormone replacement therapy
Lee, 2011, Taiwan [36]	Cohort	MW	Any site	339	Metformin ^a	No metformin	0.12 (0.08–0.19)	Age, gender, other oral antidiabetic agents, CCI
			Esophagus	27			0.44 (0.07–2.61)	
			Stomach	34			1.41 (0.42–4.73)	
			Colon and rectum	56			0.36 (0.13–0.98)	
			Liver	73			0.06 (0.02–0.16)	
			Pancreas	28			0.15 (0.03–0.79)	
Monami, 2011, Italy [37]	Case control	MW	Any site	112	Metformin	No metformin	0.46 (0.25–0.85)	Age, gender, CCS, use of insulin glargine
					Sulfonylurea	No sulfonylurea	0.75 (0.39–1.45)	
Tseng, 2011, Taiwan [38]	Cohort	M	Prostate	471	Metformin	No metformin	0.79 (0.56–1.11)	Age, diabetes duration, comorbidities, medications, occupation, PSA
					Sulfonylurea	No sulfonylurea	1.07 (0.78–1.46)	
Yang, 2011, China [39]	Cohort	MW	Any site	129	Metformin	No metformin	0.30 (0.13–0.70)	Age, gender, smoking, BMI, other drugs use, diabetes duration, A1C, systolic blood pressure at enrollment; estimates stratified according to cholesterol level (<1; ≥1 mmol/L)
							0.51 (0.31–0.82)	

^aPatients treated in monotherapy regimen.
Abbreviations: A1C, glycated hemoglobin; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; M, men; MW, men and women together; NSAID, nonsteroidal anti-inflammatory drugs; PSA, prostate-specific antigen; RR, relative risk; W, women.

for use of sulfonylurea and the risk of specific cancer sites, as well as for sulfonylurea compared with single reference therapies, were not considered because of the limited number of studies investigating these issues.

There was evidence of publication bias for studies investigating use of metformin and cancer risk either from visualization of the funnel plot (Fig. 5A) and from the corresponding Egger's test ($p = .008$), thus suggesting that studies reporting strong protective effects were more likely published. Conversely, visualization of the funnel plot (Fig. 5B) suggests that studies reporting an increased risk of cancer among sulfonylurea users are more frequently published, although the Egger's test ($p = .102$) does not detect the presence of publication bias for studies investigating the use of sulfonylurea and cancer.

DISCUSSION

In this comprehensive meta-analysis, metformin was associated with a 39% significantly decreased risk of cancer compared with no use of metformin, whereas there was no evidence that sulfonylurea was associated with cancer risk. When specific cancer sites were analyzed separately, metformin was associated with a reduced risk of colorectal and pancreatic cancers of 36% and 62%, respectively. There was no evidence that use of metformin was associated with the risk of breast and prostate cancer.

Metformin might be associated with carcinogenesis through direct and indirect (reducing hyperinsulinemia and glycemic levels) mechanisms. Hyperinsulinemia was associ-

ated with increased cancer risk at many sites including colorectal, liver, gallbladder, pancreas, and endometrial [40–44]. High glycemic levels are also considered a risk factor for selected cancers including colon and breast [40, 41].

Consistently, high levels of C-peptide/insulin and glycaemia have been associated with colorectal and pancreatic cancers in a recent meta-analysis [45]. Direct mechanisms have been also implicated in preclinical studies showing that metformin can inhibit the growth of cancer cell in vitro and in vivo [46–50]. It is therefore not surprising that the use of metformin is associated with a decreased risk of cancer, and in particular of colorectal and pancreatic cancer. The inverse relation for colorectal cancer was not noticed in a previous meta-analysis [16], which however included only three studies.

A protective effect of metformin on breast cancer was expected because metformin showed a significant growth cell inhibitory effect in mouse and cancer cell models. A study based on cell culture highlighted that metformin seems to inhibit the proliferation of cancer cells including breast cancer [9]. However, the results of this meta-analysis do not support a reduced risk of breast cancer in metformin users consistently with another meta-analysis [16].

To the best of our knowledge, no other meta-analyses have been performed on the use of sulfonylurea and cancer risk. Sulfonylurea has been associated with elevated cancer risk [27, 32, 51–53], but this might due to the nature of the comparator group. A large portion of patients who were not on therapy with sulfonylurea (that is, those included in the reference ther-

Figure 2. Forest plot of study-specific relative risk estimates for any cancer site when comparing use of metformin versus various reference therapies by study design. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; p -values are from testing for heterogeneity across study-specific estimates.

Abbreviations: CI, confidence interval; RR, relative risk.

Figure 3. Forest plot of study-specific relative risk estimates for use of metformin, versus all reference therapies, and specific sites of cancer. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; p -values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk.

Figure 4. Forest plot of study-specific relative risk estimates for any site of cancer when comparing use of sulfonylurea versus all reference therapies. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; p -values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk.

apy group) were on metformin therapy, and increased cancer risk by comparing users of sulfonylurea with those on metformin is possible. On the other hand, a reduced cancer risk is expected by comparing sulfonylurea and other antidiabetic therapies, such as insulin. This is in line with the 46% risk reduction of hepatocellular carcinoma for users of sulfonylurea with respect to insulin users reported by the only study investigating the issue [31]. This possible association, however, should be further investigated.

As with all meta-analyses of observational studies, our results have some limitations. First, they are vulnerable to confounding inherent in the original studies. We investigated the heterogeneity resulting from adjustment of original estimates for confounders. Studies reporting unadjusted estimates found a higher protective effect for metformin than those reporting adjusted estimates. However, the clinical characteristics of diabetic patients treated with metformin are different from those of patients treated with other medications, and particularly

Figure 5. Funnel plot for publication bias in the study investigating cancer risk associated with use of metformin (A) and sulfonylurea (B). Abbreviations: RR, relative risk; SE, standard error.

those treated with insulin. Thus, even correcting for a large number of covariates, it is not possible to entirely eliminate the potential of residual confounding and, in particular, confounding by indication [54, 55]. Patients treated with metformin are likely to have less severe diabetes and/or shorter disease duration compared to patients treated with other antidiabetic drugs [56]. Consequently, we cannot exclude that part of the protective effect of metformin can be explained by confounding by indication. In the sulfonylurea studies, adjustment of estimates did not substantially modify the cancer risk, supporting the conclusion that there is no increased risk of cancer. Second, in the metformin studies, the comparator group consisted of diabetics treated with no metformin, insulin, or insulin secretagogues (sulfonylurea): the similarity of the results irrespective of the nature of the comparator suggests that this did not importantly affect our estimates. Third, the study populations included were heterogeneous, particularly with regard to their

ethnicity. No evidence of heterogeneity was however noticed when we investigated the geographic area where the study was conducted (data not shown). Finally, we found evidence for selective inclusion of studies reporting higher protective effect of metformin on the cancer risk. The publication bias could be related to the use of MEDLINE as the only source for literature research, as well as to the exclusion of “grey literature” (for example, Ph.D. theses and conference abstracts) and of studies published in a language different from English.

CONCLUSION

The present meta-analysis offers quantitative evidence that oral antidiabetic drugs have different effects on cancer risk in patients with type 2 diabetes. In particular, important risk reductions for users of metformin, mainly for pancreatic and colorectal cancer, contrasted by a substantial independence from use of sulfonylurea, were noticed. Our findings, on the

protective effect of metformin, confirm the findings reported in a previous meta-analysis based on 11 studies, reporting a total of 4,042 cancer events and 529 cancer deaths [16]. In light of the exploding global epidemic of diabetes, there is a pressing need for implementing diabetes treatment with potentially protective effect against cancer. Better-designed studies on the complex interactions between diabetes, diabetes therapies, and cancer are also urgently required.

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