

## Metformin and Cancer Risk in Diabetic Patients: A Systematic Review and Meta-analysis

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### Abstract

Metformin, an insulin-lowering agent, has been associated with decreased cancer risk in epidemiologic studies in diabetic patients. We performed a comprehensive literature search and meta-analysis of epidemiologic studies to assess the effect of metformin on cancer incidence and mortality in diabetic patients, using Pubmed, ISI Web of Science, Embase, and the Cochrane library until May 2009, with no language or time restrictions. Independent reports with sufficient information to allow risk estimation of cancer risk/mortality and a measure of uncertainty were reviewed and cross-checked independently by three investigators. Eleven studies were selected for relevance in terms of intervention, population studied, independence, and reporting of cancer incidence or mortality data, reporting 4,042 cancer events and 529 cancer deaths. A 31% reduction in overall summary relative risk (0.69; 95% confidence interval, 0.61-0.79) was found in subjects taking metformin compared with other antidiabetic drugs. The inverse association was significant for pancreatic and hepatocellular cancer, and nonsignificant for colon, breast, and prostate cancer. A trend to a dose-response relationship was noted. Metformin is associated with a decreased risk of cancer incidence compared with other treatments among diabetic patients. Given the retrospective nature of most studies and the possibility that the control treatments increase risk, phase II trials are needed before large cancer prevention trials are launched. *Cancer Prev Res*; 3(11); 1451-61. ©2010 AACR.

### Introduction

A large proportion of all cancers in Western countries is attributable to Western lifestyle, characterized by physical inactivity and early onset of metabolic syndrome and insulin resistance with diabetes, cardiovascular disease, and cancer (1-7). Hyperinsulinemia adversely affects prognosis in cancer patients (3, 7-11) and is an independent risk factor for several types of neoplasms, thus explaining the obesity-cancer association (12). Insulin can promote tumorigenesis through a direct effect on epithelial tissues acting on the insulin/insulin-like growth factor family of receptors (13), or indirectly by affecting the levels of other modulators, such as insulin-like growth factors, sex hormones, and adipokines (14, 15). Recent evidence indicates that the abnormally high proliferative

activity of premalignant and malignant cells requires high levels of nutrients to meet the increased demands for energy consumption and protein biosynthesis (16). Aberrations of genes involved in the metabolic pathways, such as the AMPK/LKB1 pathway, thus represent an emerging hallmark of carcinogenesis that is increasingly being recognized as a plausible preventive and therapeutic target (17).

Metformin is the drug of choice for the management of type 2 diabetes mellitus (18). It improves insulin resistance and glycemic control and can safely be combined with other classes of antidiabetic agents (19). Its primary action is to inhibit hepatic glucose production through an LKB1/AMPK-mediated mechanism; however, it also improves insulin sensitivity in peripheral tissues (19-21). Metformin lowers cardiovascular mortality by ~25% compared with other oral diabetic treatments or placebo (22) and was able to reduce the incidence of diabetes in persons at high risk (23), with beneficial effects persisting for at least 10 years (24). It has good safety profile and is well tolerated in subjects with normal glycemic levels (25), with transient nausea and diarrhea being the most evident side effects (26). Importantly, its cost is extremely low (in the order of a few cents per tablet), thus being easily accessible in clinical practice.

Interest in metformin in cancer prevention and treatment reflects the recent convergence of several areas of research (27). Exciting preclinical studies have shown that

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metformin can inhibit the growth of cancer cells *in vitro* and *in vivo* (27–31). The recent evidence that metformin results in (a) initiation of an LKB1-mediated AMPK-dependent energy stress response that can adversely affect survival of cancer cell lines (28, 32) and (b) inhibition of phosphoinositide 3-kinase/Akt/mammalian target of rapamycin signaling, leading to reduced proliferation of cancer cell lines (32), has provided a molecular basis for a direct, insulin-independent antitumor effect and strengthened the rationale to evaluate metformin in cancer clinical trials (26, 33).

Metformin has been associated with cancer risk reduction in recent epidemiologic studies in diabetic patients (34–46). With these premises, we performed a systematic review and meta-analysis of available studies to better define the effect of metformin on cancer incidence and mortality in diabetic patients.

## Materials and Methods

The search was carried out on observational studies and trials, and no language or time restrictions were applied. The literature from January 1, 1966, to May 31, 2009, was searched using the following databases: Pubmed, ISI Web of Science (Science Citation Index Expanded), Embase, and the Cochrane library. The following main keywords or corresponding MeSH terms were used: “Metformin,” “Biguanides,” or “Diabetes Mellitus, Type 2/therapy” and “cancer” or “neoplasms.” A manual search was also done for references cited in the selected articles, and in selected reviews or books.

Criteria for inclusion of an article in the analysis were as follows: (a) to be the principal published report of an observational study or clinical trial (highest number of patients included) evaluating treatment with metformin on cancer incidence or mortality; (b) to be independent from other studies to avoid giving double weight to estimates derived from the same study; (c) to have sufficient information to allow adequate estimation of the hazard ratio (HR)/relative risk (RR) and 95% confidence intervals (95% CI; i.e., crude data or adjusted estimates and SEM, confidence intervals or *P* values) to estimate cancer risk under metformin compared with other antidiabetic treatments or no treatment.

The participant flow diagram for the study inclusion in the meta-analysis is shown in Fig. 1. A total of 13 articles (34–46) were retrieved and checked for relevance in terms of intervention, population studied, and reporting of cancer incidence data. Eight of these articles were not included in the meta-analysis for the following reasons: (a) two referred to the same study cohort: Evans et al. (35) presented a subset of patients included in a study published later (36), and Jecht (37) published in a German language journal the results already presented in English by Libby et al. (36); (b) six did not report overall cancer incidence but data on a single organ site, that is, pancreatic cancer (38), hepatocellular cancer (HCC; refs. 34, 45), breast (46), prostate (39), and colorectal cancer (40). These stud-

ies were analyzed separately for descriptive purposes. Two studies (41, 42) presented data on cancer mortality only and were included in the main meta-analysis, evaluating their exclusion in the sensitivity analysis. The comparators were sulfonylureas, insulin, or other (sometimes not specified) diabetic treatments, including thiazolidinediones and meglitinides. The population under study was formed by patients with diabetes.

We extracted fully adjusted HR or odds ratios (OR) and their CIs, and we calculated the corresponding variance using the formula proposed by Greenland (47). Association between metformin and cancer incidence/mortality across selected studies was computed as a summary RR (SRR) with 95% CI. We assessed the homogeneity of the effect across studies using the large sample test based on the  $\chi^2$  statistic. Because the  $\chi^2$  test has limited power, we considered that statistically significant heterogeneity existed when the *P* value was  $\leq 0.10$ . Heterogeneity was also evaluated using the  $I^2$  parameter, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance. Subgroup analyses and meta-regressions were carried out to investigate between-study heterogeneity, evaluating the influence of study and population features on the risk estimates. Sensitivity analyses were carried out to verify the effect of inclusion and exclusion criteria on the stability of the estimates. The SRR was estimated, pooling the study-specific estimates by random-effects models fitted using SAS (Proc Mixed) with maximum likelihood estimates.

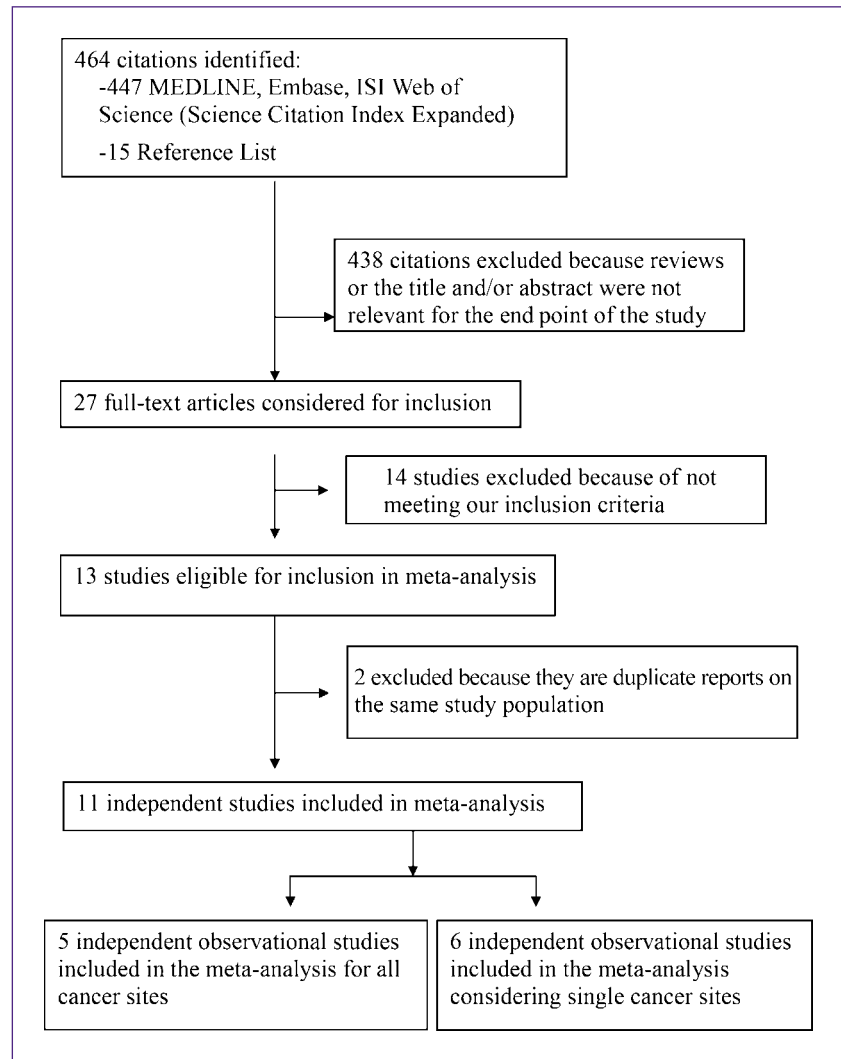
Pooled estimates for the dose-response models evaluating the effect of metformin by time of use were obtained with a two-step procedure. In the first step, a linear model was fitted within each study to estimate the RR per 1 year of increase. When sufficient information was published (the number of subjects at each category of serum level categories), the model was fitted according to the method proposed by Greenland and Longnecker (48), which provides the natural logarithm of RR, and an estimator of its SEM, taking into account the fact that the estimates for separate categories depend on the same reference group. When number of subjects at each category was not available from the articles, coefficients were calculated, ignoring the correlation between the estimates of risk in the separate exposure levels. In the second step, the summarized RR was estimated, pooling the study-specific estimates by the classic random-effects models.

To verify whether publication bias might affect the validity of the estimates, funnel plots were investigated, considering regression of  $\ln(\text{RR})$  on the sample size, weighted by the inverse of the pooled variance (49). All analyses were done with SAS software version 8.02 (SAS Institute, Inc.) and STATA software version 10 (Stata, Inc.).

## Results

The main characteristics of the 11 studies included in the present analysis are reported in Table 1, and risk

**Fig. 1.** Flowchart of selection of studies for inclusion in meta-analysis.



estimates for cancer incidence and mortality for any site and for specific sites are reported in Table 2. All studies except one prospective study were retrospective, eight were case-control, and three were cohort studies conducted between 1987 and 2009 and published between 2004 and 2010 on a total of 4,042 cases of cancer events and 529 cancer deaths. Seven studies were conducted in Europe, three in the United States, and one in Canada. Four studies (34, 38, 39, 45) also included a subgroup of nondiabetic patients.

The summary risk estimates for metformin and cancer risk are plotted in Fig. 2. A significant inverse relationship between metformin use and cancer incidence or mortality was found, with a reduction of 31% in subjects taking metformin compared with other antidiabetic compounds (SRR, 0.69; 95% CI, 0.61-0.79). There was evidence for some heterogeneity among studies ( $P = 0.03$  and  $I^2 = 64\%$ ). The Macaskill regression test showed no evidence for publication bias ( $P = 0.12$ ). Mean age was not significant when it was included in the meta-regression model ( $P = 0.29$ ).

When we carried out the analysis separately by type of end point, we summarized three estimates for cancer incidence and three for mortality from a total of five studies, and found similar SRRs with a decrease in heterogeneity for mortality: SRR 0.68 (95% CI, 0.52-0.88) with  $P = 0.02$  and  $I^2 = 74\%$  for cancer incidence, and SRR 0.70 (95% CI, 0.51-0.96) with  $P = 0.14$  and  $I^2 = 50\%$  for mortality. The difference between cancer incidence and cancer mortality SRRs was not statistically significant ( $P = 0.90$ ).

After inclusion of the studies by Li et al. (38), Donadon et al. (34), Hassan et al. (45), Bodmer et al. (46), Wright and Stanford (39), and Yang et al. (40), which provided data on pancreatic, HCC, breast, prostate, and colon cancer incidence, respectively, we also found similar summary estimates: SRR 0.55 (95% CI, 0.42-0.70). Dose-response analysis, evaluating the effect of metformin by duration of use, indicated that the effect increased by each year of use: SRR 0.77 (95% CI, 0.55-1.09;  $\chi^2 P = 0.01$  and  $I^2 = 77\%$ ) for 1 year of use, SRR 0.60 (95% CI, 0.30-1.19) for 2 years, and SRR 0.28 (95% CI, 0.05-1.55) for 5 years.

**Table 1.** Epidemiological studies of metformin and cancer risk

Source (Country)	Design & population	Site of cancer*	Mean age (yrs)	Period	Ca incidence/ Ca mortality	No of cases	No of controls	Mean f-up (yrs)
Yang et al., 2004 (UK) (40)	Nested case-control study on type II diabetes patients	Colon	75	1987-2002	Yes/No	125	1195	3.9
Bowker et al., 2006 (Canada) (41)	Population-based, retrospective cohort study on type II diabetes patients	Any site	63	1991-1996	No/Yes	407	10309 <sup>†</sup>	5.4
Monami et al., 2008 (Italy) (43)	Hospital-based, case-control study on type II diabetes patients	Any site	69	1998-2005	Yes/No	195	195	6.5
Libby et al., 2009 (Scotland, UK) (36)	Population-based, historical cohort study on type II diabetes patients	Any site	66	1994-2003	Yes/Yes	771	8170 <sup>†</sup>	7
Currie et al., 2009 (UK) (44)	General practices, retrospective cohort study on type II diabetes patients	Any site	64	2000-2005	Yes/No	373	7897 <sup>†</sup>	2.4
Donadon et al., 2009 (Italy) (34)	Hospital Based Case-Control study	HCC	na	1994-2006	Yes/No	465	490	na
Landman et al., 2009 (Netherlands) (42)	General practice based cohort study on type II diabetes patients	Any site	68	1998-2009	No/Yes	122	1353 <sup>†</sup>	9.6
Wright et al., 2009 (USA, WA) (39)	Population-based, case-control study	Prostate	60	2002-2005	Yes/No	1001	942	5
Li et al., 2009 (USA, TX) (38)	Hospital-based, case-control study	Pancreas	61	2004-2008	Yes/No	973	863	na
Hassan et al., 2010 (USA, TX) (45)	Hospital-based, case-control study	HCC	62	2000-2008	Yes/No	122	86	na
Bodmer et al., 2010 (UK) (46)	Nested case-control study on type II diabetes patients	Breast	68	1994-2005	Yes/No	17	120	na

\*Site cancer included in the analysis; HCC: hepatocellular carcinoma.

<sup>†</sup>Persons at risk; na: data could not be retrievable from the published paper.

Regarding specific organ sites, we were able to obtain a summary risk estimate for colon and breast cancer, for which we found three studies each. For the other cancer sites, we have just described and discussed the results as presented in the articles. Significant reduced risk estimates for metformin use were found for pancreatic cancer and HCC, whereas there were nonsignificant trends for colon, breast, and prostate cancer (Table 2).

Specifically, for colon cancer, Yang et al. (40) found no effect of metformin on risk when used alone (OR, 1.0; 95% CI, 0.6-1.7) or in combination with sulfonylureas (OR, 1.2; 95% CI, 0.7-2.2), whereas Currie et al. (44) found a lower risk in metformin users compared with sulfonylurea users (HR, 0.56; 95% CI, 0.40-0.76) or insulin-based-treatment users (HR, 0.59; 95% CI, 0.43-0.81).

Also, Libby et al. (36) observed a significant risk reduction when comparing metformin users versus nonusers on colon cancer incidence (HR, 0.6; 95% CI, 0.38-0.94). The summary risk estimate for metformin and colon cancer risk is plotted in Fig. 3 (top). Again, we found an inverse association between metformin use and colon cancer incidence, although not significant (SRR, 0.64; 95% CI, 0.38-1.08;  $P$  for heterogeneity = 0.17,  $I^2$  = 44%).

For pancreatic cancer, Currie et al. (44) found a highly significant risk reduction in metformin users compared with sulfonylurea users (HR, 0.20; 95% CI, 0.11-0.36) and with insulin-based-treatment users (HR, 0.22; 95% CI, 0.12-0.38). Likewise, a significant risk reduction was noted by Li et al. (38) when comparing metformin users versus nonmetformin users (OR, 0.38; 95% CI, 0.21-0.67).

With regard to HCC, Donadon et al. (34) found a reduced risk for HCC in subjects taking metformin versus insulin or sulfonylureas (OR, 0.33; 95% CI, 0.1-0.7), and Hassan et al. (45) found similar associations when metformin users were compared with nonusers (OR, 0.3; 95% CI, 0.2-0.6).

Concerning breast cancer, Libby et al. (36) found a non-significant trend for a protective effect on metformin users versus nonusers (HR, 0.6; 95% CI, 0.32-1.10), whereas Currie et al. (44) noted a weak trend when metformin was a concomitant treatment among glargine users versus all other insulin regimens (HR, 0.88; 95% CI, 0.48-1.63), or when metformin was given as a monotherapy versus insulin-based regimens (HR, 0.93; 95% CI, 0.69-1.27). No effect was found when metformin monotherapy was compared with sulfonylureas (HR, 1.02; 95% CI, 0.71-1.45). Bodmer et al. (46) found a significant protective effect (OR, 0.44; 95% CI, 0.24-0.82) among long-term users of metformin, defined as 40+ prescriptions (~5+ years). The summary risk estimate for metformin and breast cancer risk is plotted in Fig. 3 (bottom). A non-significant inverse association of metformin and breast cancer incidence was found (SRR, 0.70; 95% CI, 0.28-1.77;  $P$  for heterogeneity = 0.05,  $I^2$  = 68%).

For prostate cancer, Wright and Stanford (39) found a borderline significant protective effect of metformin users versus nonusers (OR, 0.56; 95% CI, 0.32-1.00), whereas Currie et al. (44) found only a weak trend (HR, 0.93; 95% CI, 0.67-1.32, and HR, 0.91; 95% CI, 0.66-1.27) when metformin monotherapy was compared with sulfonylurea and insulin regimens, respectively.

## Discussion

The main analysis, based on five observational studies, shows that metformin is associated with a 31% statistically significant decrease in cancer risk compared with other diabetic treatments, although with some degree of heterogeneity among studies. When analysis was done separately by cancer incidence and cancer mortality, we found similar SRRs with a decrease in heterogeneity for mortality and no statistically significant difference ( $P$  = 0.90) between the two estimates. When the six studies on incidence of single cancer sites, that is, colon (40), pancreatic (38), HCC (34, 45), breast (46), and prostate (39) cancers, were included, similar summary risk estimates were obtained (SRR, 0.55; 95% CI, 0.42-0.70). A trend toward a large risk reduction was noted for colon and pancreatic cancer (60-80% risk reduction) in two independent studies for each cancer site, even when only those cancers diagnosed >2 years after diabetes developed were included (to minimize effects of reverse causation). Two studies showed a significant trend for metformin on HCC (34, 45), whereas risk estimates were not statistically significant for colon, breast, and prostate cancer. A dose duration-response relationship was noted, although it was not statistically significant probably due to low power and heterogeneity of the end points (only three studies evaluating different cancer sites).

Metformin has been shown to interfere with carcinogenesis through indirect and direct mechanisms. Hyperinsulinemia increases cancer risk in healthy subjects and can partly explain the obesity-cancer risk association in many organ sites, including colon, breast (postmenopausal), endometrial, gallbladder, pancreatic, kidney, and esophageal cancers (3-5, 50, 51). High glycemic levels are also a risk factor for several cancers, including colon and breast (2, 3). However, direct antitumor mechanisms for metformin have been implicated because preclinical studies have shown that metformin can inhibit the growth of cancer cells *in vitro* and *in vivo*. In preclinical models, a key mechanism of the antitumor effect of metformin is through activation of the AMPK pathway, a central cellular key energy sensor allowing cell division, which is a highly energy-consuming process, only if cells have sufficient metabolic resources (52, 53). AMPK, which is also activated by weight loss and physical activity (54, 55), once activated leads to suppression of many of the metabolic processes that highly depend on sufficient cellular ATP supply (gluconeogenesis, protein and fatty acid synthesis, cholesterol biosynthesis) and that promote catabolic processes (glycolysis, fatty acid  $\beta$  oxidation; ref. 56). Mechanistically, AMPK achieves this by raptor-dependent phosphorylation and stabilization of the protein product of the tuberous sclerosis complex tumor suppressor gene-2 (54, 55, 57), which serves as an integrator of various regulatory inputs implicated in cell growth and transmits them to the master regulator of cellular protein synthesis, the mammalian target of rapamycin (56).

Because all studies but one (42) were retrospective, the findings provided by this meta-analysis should be viewed with caution, although four studies were based on objective record linkage datasets (37, 40, 41, 44, 46). Another issue is the potential residual confounding and the allocation bias, with metformin users being at different stage of diabetes and baseline risk of cancer than comparators. For instance, all cohort studies (36, 41, 42, 44) showed that metformin was started at a younger age compared with other diabetic drugs, likely because of treatment guidelines (58), and in subjects with higher body mass index, possibly because of its weight-lowering effects (59). However, most studies were adjusted for these confounders, thus minimizing the potential bias. Another limitation was that some case-control studies were hospital based (38, 43, 45) and therefore may not fully represent the general population of diabetic patients.

The nature of the comparator group, which was mainly composed of diabetic patients treated with insulin and insulin secretagogues (sulfonylureas), should be taken into proper account when interpreting the results of the current study. Both classes of agents increase insulin levels, and sulfonylureas have been associated with higher cancer risk (41, 60, 61). Likewise, insulin, particularly glargine, has been associated with an increased cancer risk in some (62-65), but not all (66, 67), epidemiologic studies; thus, the true protective effect of metformin cannot be estimated. The observation that a different class of

**Table 2.** Risk estimates for metformin and cancer risk

Source (Country)	Treatment comparison	Risk estimates and 95%CI	Adjusting variables (other than age & sex)
Yang et al., 2004 (UK) (40)	3+ years of metformin users vs. not users combination metformin + sulphonylureas	Colon: 1.0 (0.6-1.7)* Colon: 1.2 (0.7-2.2)	Smoking, history of cholecystectomy, diabetes duration, BMI, insulin use, sulphonylurea use, aspirin/NSAID use
Bowker et al., 2006 (Canada) (41)	sulphonylureas and exogenous insulin users	For any site: 0.77 (0.63-0.91)*	Insulin use, comorbidity
Monami et al., 2008 (Italy) (43)	other hypoglycaemic drugs users	For any site and –at any time: 0.6 ( $P > 0.05$ ) –at least 12 months: 0.33 ( $P < 0.001$ ) –at least 36 months: 0.28 (0.13-0.57)*	Smoking, alcohol use, comorbidity, BMI, HbA1c, diabetes duration, concomitant hypoglycemic treatment
Libby et al., 2009 (Scotland, UK) (36)	non metformin users	Overall cancer: 0.63 (0.53-0.75)* Bowel cancer: 0.6 (0.38-0.94); Lung cancer: 0.7 (0.43-1.15); Breast cancer: 0.6 (0.32-1.10) Cancer incidence by maximum dose, ≥4 y. of f-up <sup>†</sup> : Low, 0.16 (0.06-0.44); Medium, 0.4 (0.27-0.60); High, 0.15 (0.09-0.25). Cancer mortality: 0.63 (0.49-0.81)*	Smoking, BMI, HbA1c, material deprivation, other drug use (sulphonylureas or insulin)
Currie et al., 2009 (UK) (44)	metformin monotherapy vs. sulfonylureas monotherapy	All solid tumors: 0.74 (0.65-0.84)* For breast: 1.02 (0.71-1.45); For colon: 0.56 (0.40-0.76) For pancreatic: 0.20 (0.11-0.36); For prostate: 0.93 (0.67-1.32)	Smoking, comorbidity, HbA1c, diabetes duration, weight
	metformin monotherapy vs. insulin-based treatment	All solid tumors: 0.70 (0.63-0.79) For breast: 0.93 (0.69-1.27); For colon: 0.59 (0.43-0.81) For pancreatic: 0.22 (0.12-0.38); For prostate: 0.91 (0.66-1.27)	

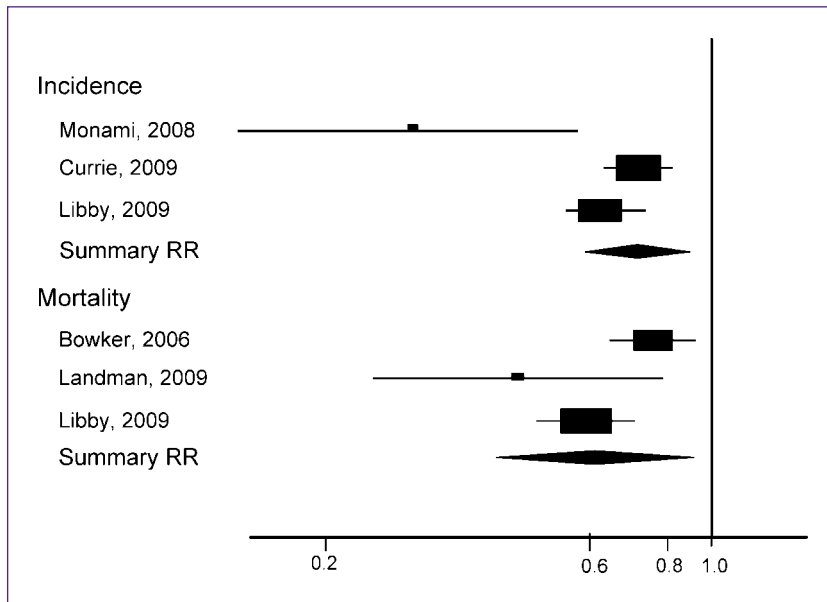
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**Table 2. Risk estimates for metformin and cancer risk (Cont'd)**

Source (Country)	Treatment comparison	Risk estimates and 95%CI	Adjusting variables (other than age & sex)
Donadon et al., 2009 (Italy) (34)	insulin or sulphonylureas users	Metformin use for hepatocellular cancer among diabetic patients: 0.33 (0.1-0.7)	no adjusting variables were considered
Landman et al., 2009 (Netherlands) (42)	non metformin users	Overall cancer mortality: 0.43 (0.23-0.80)*; –for every one gram increase in the metformin dosage: 0.58 (0.36-0.93).	Smoking, diabetes duration, HbA1c, serum creatinine, BMI, blood pressure, total cholesterol/HDL, albuminuria, insulin use, sulphonylurea use and macrovascular complications
Wright et al., 2009 (USA, WA) (39)	non metformin users	Metformin use for prostate cancer: –among Caucasians 0.56 (0.32-1.00)* –among African-Americans 1.62 (0.53-5.02) –diabetes vs no diabetes: 0.66 (0.39-1.11)	BMI, statin and aspirin use, other diabetes treatment, PSA screening history, family history of PCa
Li et al., 2009 (USA, TX) (38)	non metformin users	Metformin use for pancreatic cancer: –all subjects: 0.38 (0.21-0.67)* –among diabetic patients only: 0.38 (0.22-0.69). –never users of insulin: 0.44 (0.22-0.87). –duration of diabetes >2 years: 0.41 (0.19-0.87).	Smoking, alcohol use, BMI, duration of diabetes, insulin use, family history of cancer, race
Hassan et al., 2010 (USA, TX) (45)	non metformin users	Metformin use for hepatocellular cancer among diabetic patients: 0.3 (0.2-0.6)	Race, educational level, cigarette smoking, alcohol drinking, hepatitis C virus, hepatitis B virus, family history of cancer
Bodmer et al., 2010 (UK) (46)	non metformin users	Long metformin use (40+prescriptions) for breast cancer among diabetic patients: 0.44 (0.24-0.82)	General practice and calendar time by matching, other use of prandial glucose regulators, acarbose, estrogens, smoking, BMI, diabetes duration and HbA1c

\*Estimates included in the meta-analysis (when more than one estimates were considered).

†The authors presented also the estimates for shorter follow-up.



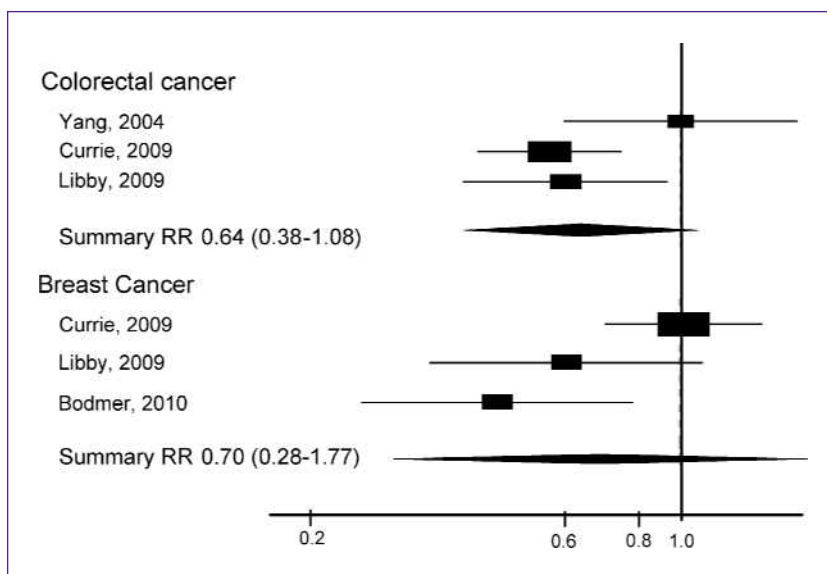
**Fig. 2.** Forest plot of the association between metformin and cancer incidence or mortality.

insulin-lowering agents such as thiazolidenediones were not associated with reduced cancer risk in two studies suggests that the full anticancer effect of metformin is not due solely to reductions in insulin or that thiazolidenediones have cancer-promoting effects that counteract the reductions in insulin that are usually seen with those agents.

Lastly, our study does not address the issue in nondiabetic populations at risk for cancer for different conditions, including personal or family history of cancer or the presence of premalignant lesions, in which the preventive potential of metformin is unknown. However, because diabetes and obesity are emerging risk factors, involving a large fraction of the population of Western

countries (1, 4–6), the findings derived from this meta-analysis may have important public health implications.

The finding that metformin is associated with lower cancer risk in different organ sites could be explained with the notion that metformin is operating through the lowering of the uptake and utilization of nutrients into the biomass needed to produce a new cell from an active proliferating cell (16). This general mechanism of inhibition of the signaling pathways implicated in actively proliferating cell renders metformin particularly attractive as a part of a global prevention strategy in a large group of high-risk individuals, for example, subjects with metabolic syndrome with multiple risk for different major diseases, including cardiovascular disease, diabetes, and cancer (68, 69). On



**Fig. 3.** Forest plot of the association between metformin and colon and breast cancer incidence.



the other hand, the observation that metformin was associated with greater risk reduction in specific major cancer killers such as colon, pancreatic, and breast cancer is consistent with the notion that diabetes or elevated insulin and glucose levels play an important role in the development of these tumors (2, 3, 7) and has important clinical research implications. For instance, metformin has been shown to reverse the effects of the high-energy diet on the growth of colon cancer cells (70, 71) and, in a recent pilot clinical trial on 26 nondiabetic patients with aberrant crypt foci, metformin at a dose 250 mg/d for 1 month suppressed the mean number of aberrant crypt foci per patient, compared with control/untreated subjects (72). Moreover, metformin can prevent the promotional effect of high-fat diet on pancreatic carcinogenesis in the hamster (73) and inhibits pancreatic cancer growth in nude mouse xenografts (74). A tissue-based biomarker clinical trial in individuals at risk for pancreatic cancer due to genetic predisposition or premalignant disorders could be considered. As for breast cancer, metformin at low doses was shown to inhibit cellular transformation and selectively killed cancer stem cells in four genetically different types of breast cancer (75), including inhibition of transformation of MCF10A-ER-Src cells, a dysplastic cell line. Several presurgical window of opportunity trials are currently under way to assess the antiproliferative effect of metformin on malignant, premalignant, and hyperplastic breast cells (33).

The association of metformin with reduced cancer mortality noted in three studies (36, 41, 42) provides the rationale for the study of metformin in the cancer treatment setting. Although data on the prognostic charac-

teristics of these tumors and the specific type of treatments were not available, a potential synergistic effect of metformin and antineoplastic therapy cannot be excluded. In support of this hypothesis, a recent retrospective study (76) in breast cancer patients showed that diabetic cancer patients treated with metformin and neoadjuvant chemotherapy had a higher pathologic complete response rate than the control groups. A phase III adjuvant trial of metformin is being launched by National Cancer Institute Canada and National Cancer Institute United States (study NCIC MA32) to assess the efficacy of metformin in reducing breast cancer recurrence in 3,582 women with stage I and II breast cancer (26).

In conclusion, our study indicates that metformin is associated with a 30% reduction in cancer incidence in individuals with type 2 diabetes compared with other diabetic treatments. Promising trends were noted on overall cancer mortality and on specific cancer sites, particularly pancreatic cancer and HCC and, to a lesser extent, colon and breast cancers. Finally, this analysis supports further research on the cancer-preventive potential of metformin.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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