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# Metformin effects revisited

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## Abstract

Metformin is a cornerstone in the treatment of type 2 diabetes. Although its mechanism of action is not well understood, there is new evidence about its possible role in cancer. A Pubmed search from 1990 to 2011 was done using the terms metformin, cancer, mechanism of action, diabetes treatment and prevention. We found more than one thousand articles and reviewed studies that had assessed the efficacy of metformin in treatment and prevention of type 2 diabetes and its mechanisms of actions, as well as articles on its antitumoral effects. We found that the United Kingdom Prospective Diabetes Study and the Diabetes Prevention Program have demonstrated the efficacy of metformin in terms of treatment and prevention of type 2 diabetes; metformin is safe, cost effective and remains the first line of diabetes therapy with diet and exercise. The mechanisms of action include a decrease of hepatic insulin resistance, change in bile acids metabolism, incretins release and decreased amyloid deposits. The AMP-activated protein kinase seems to be an important target for these effects. Epidemiological retrospective studies point out a possible association between metformin and decreased cancer risk, data supported by in vitro and animal studies. These data should trigger randomized controlled trials to prove or disprove this additional benefit of metformin.

### Keywords

Metformin; Biguanides; Cancer; Type 2 diabetes

## 1. Introduction

The prevalence of type 2 diabetes (T2DM) is rapidly increasing worldwide [1], mostly due to obesity, so cheap and effective treatments are essential. Metformin is one of the most used oral glucose-lowering drugs for the treatment of T2DM [2]. The two main biguanides, metformin and phenformin were introduced for the first time in the late 1950s, but phenformin had to be withdrawn because of a strong association with lactic acidosis.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

Metformin can increase lactate oxidation but not change the release of lactate from muscle or plasma lactate concentration [3,4], so its association with lactic acidosis is very rare.

In the U.S.A., metformin became available in the 1990s. Previously, metformin was shown to lower blood glucose in randomized placebo-controlled studies [5], specifically by lowering fasting plasma glucose by decreasing hepatic glucose output and improving muscle sensitivity to insulin [3].

Before metformin came on the scene, sulfonylureas were the main oral drugs prescribed in T2DM with a well demonstrated efficacy, so at the time metformin was introduced there was a debate about what drug should be the first-line treatment in T2DM. In 1995, Campbell and Howlett did a meta-analysis of published prospective, controlled and randomized trials of metformin compared to sulfonylureas [6]. They found 11 acceptable studies involving 656 patients, and reported that both medications achieved a similar glycemic control, decreasing glycosylated hemoglobin (HbA1c) by 1.2%, but there was a weight loss benefit with metformin. Bailey and Turner, in a review in 1996 [7] also concluded that metformin could achieve a similar glycemic control than sulfonylureas, but metformin did not cause weight gain, hypoglycemia or increase insulin concentrations. Up to the present, the United Kingdom Prospective Diabetes Study (UKPDS) [8] is the most important study assessing metformin compared with other treatments; and the Diabetes Prevention Program (DPP) the most relevant trial in terms of diabetes prevention [9].

So actually, although there are many different medications to treat T2DM, metformin is still a cornerstone in the T2DM therapy. In fact, a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes, recommend metformin as the first step in T2DM treatment, if there is not a contraindication [10]. Despite the length of its use, continuing research on metformin's mechanisms of action and particularly its potential role in cancer has restored its popularity.

## 2. United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS is a randomized, prospective and multicenter intervention trial which enrolled newly diagnosed T2DM patients between 1977 and 1991. The goal of the UKPDS was to study the effect of glycemic control on the prevention of complications, associated morbidity and mortality in non-insulin dependent diabetes, and compare diet alone with sulfonylureas, insulin and metformin [8].

Patients with fasting plasma glucose (FPG) at entry between 108 and 270 mg/dL, were randomized to sulfonylurea, insulin, metformin (only in overweight patients defined as >120% ideal body weight) or diet. At three years metformin achieved a similar reduction in FPG and glycated hemoglobin (HbA1c) as did sulfonylureas or insulin, but in addition it reduced fasting plasma insulin and did not induce weight gain [11]. Metformin was associated with fewer hypoglycemic episodes than sulfonylureas or insulin, but more than diet [12].

It was difficult to maintain an optimal glycemic control with monotherapy in the long term; in overweight patients on metformin only 39% could maintain FPG less than 140 mg/dL at three years and 34% had HbA1c < 7% at six years [13], similar to the other drug groups.

A 10-year analysis [14] showed that metformin produced a comparable glycemic control as did the other groups, without significant differences in weight but with lower fasting plasma insulin and lower hypoglycemic episodes than sulfonylureas and insulin.

### 2.1. Effect on complications

Drug therapy was associated with a lower risk of microvascular complications and reduced (not significantly) the risk of myocardial infarction. The metformin group had a lower risk of any diabetes-related endpoint (32%), diabetes related-death (42%), all-cause mortality (36%), myocardial infarction (39%) and all macrovascular diseases (30%) than did the diet group. The risk of retinopathy progression was also lower in the metformin group than in the conventional group, without differences in renal failure. Compared with the sulfonylurea and insulin groups, only the risk of diabetes-related endpoint and all-cause mortality was significantly lower in the metformin group [14].

On the other hand, in 1990 patients on sulfonylureas (overweight and non-overweight) who had FPG between 109.8 and 270 mg/dL were randomized to continue sulfonylureas alone or have metformin added to their regimen to know whether this addition had any advantage [14]. When metformin was added there was a decrease in FPG compared with the group on sulfonylureas alone; HbA1c values also decreased initially with addition of metformin but at three years were similar than in the sulfonylurea group. Surprisingly, it was found that the addition of metformin increased the risk of diabetes-related death and of any cause of death, maybe because the patients who were on sulfonylureas previously were older, more hyperglycemic and had been followed-up for a shorter time. However, a subsequent UKPDS publication [15] reported an increased life expectancy in overweight T2DM patients.

Another important issue is that metformin allows for cost-savings in overweight T2DM patients [15]. This is partly due to a lesser number of hospital days and lower cost of hospital stays in patients on metformin compared with the conventional treatment group [15].

So, UKPDS showed that metformin is as effective as sulfonylureas and insulin in glycemic control, but with no weight gain and a lower risk of hypoglycemia. However, the benefits of metformin were evaluated solely in overweight patients. An observational and retrospective study examining a database of patients on metformin or on sulfonylureas for at least for 6 months [16], concludes that metformin could be as effective as sulfonylureas in obese and non-obese patients after analyzing glycemic control and diabetes-related complications.

Ten years after the end of the UKPDS study, metformin in overweight participants was still associated with a statistically significant reduction in the risk of any diabetes-related endpoint (21%), diabetes-related death (30%), myocardial infarction (33%) and all-cause mortality (27%), compared with diet, although glycemic control was not significantly different; no differences in risk of microvascular disease were found [17].

As seen in UKPDS, metformin is a safe, cost-effective drug that achieves a good glucose control and ameliorates macrovascular risk in overweight patients with T2DM.

## 3. Diabetes Prevention Program (DPP)

Diabetes prevention is extremely important, particularly with the increased global prevalence of obesity, as more and more people are at risk of developing the disease and its associated complications, frequently present at diagnosis. DPP is the largest trial performed to assess strategies to prevent diabetes. It is a randomized trial involving more than 3000 people from 27 centers in the USA that are at high risk for diabetes: body mass index (BMI) > 24 or > 22 $kg/m^2$ in Asians; FPG: 95–125 mg/dL; 2 h glucose after 75-g oral glucose load: 140–190 mg/dL. Participants were randomized to one of three groups: standard lifestyle recommendations plus placebo, standard lifestyle recommendations plus metformin and intensive lifestyle intervention (ILS). After an average follow up of 2.8 years, diabetes incidence was 58% lower in the ILS group and 31% lower in the metformin group compared with placebo [9], showing that treatment with metformin is a good strategy for diabetes prevention (in both genders and different ethnic groups), as well as being cost-effective [18]. Metformin was more effective in persons with higher BMI [19], higher FPG [20] and in women with previous gestational diabetes [21], and improved insulin levels and weight compared with placebo. But, although metformin reduced anthropometric measurements at one year, weight, BMI and waist circumference did not predict diabetes development in the metformin group [20].

Metformin use also predicted regression from impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) to isolated IGT, but not to normal glucose tolerance [22], and improved insulin sensitivity at one year compared with placebo [23].

Metformin reduced the incidence of the metabolic syndrome in 17% of the patients, compared to placebo, an effect that was surprisingly not seen in women [24]. Although C-reactive protein and fibrinogen, possible cardiovascular risk factors, were lower in the metformin group compared to placebo [25], there were no significant differences in cardiovascular events among groups [26].

Long-term data from the DPP, obtained 10 years after randomization [27], showed that ILS and metformin were still associated with a lower diabetes incidence (34% and 18% respectively) compared with placebo. Therefore, metformin is also a good long-term strategy to prevent diabetes.

## 4. Safety

The most frequent adverse events of metformin are gastrointestinal symptoms, occurred in 22% of patients, but they usually are mild and transient [4]. Lactic acidosis is really very rare (4.3 cases per 100,000 patient-years) [28], probably due to the fact that metformin does not change plasma lactate levels [3,4,28]. Metformin can interfere with vitamin B12 levels, but anemia is not frequent [4]. Finally, in terms of hypoglycemia, metformin has demonstrated its safety [12].

## 5. Mechanisms

Metformin has been used clinically for over 50 years, but its molecular mechanism of action is not well understood. The glucose-lowering action is largely due to the improvement in hepatic insulin resistance leading to a reduction in hepatic glucose output, mainly as result of reduction in gluconeogenesis [3,29]. Metformin also increases glucose uptake in muscle, without extra lactate production, and raises insulin binding to insulin receptors (IR), while increasing the phosphorylation and tyrosine kinase activity of the IR [7]. In human hepatic cells, metformin increases insulin receptor activation independently of insulin, acting predominantly through insulin receptor substrate 2 [30].

A possible important target for metformin is AMP-activated protein kinase (AMPK), a cellular energy sensor activated under metabolic stress. The activation of AMPK inhibits glucose production by the liver, improvesinsulin sensitivity and glucose uptake by the muscle and induces fatty acid oxidation. Threonine 172 phosphorylation is necessary for this activation and the tumor suppressor gene LKB1 is the main responsible kinase. The major downstream target of AMPK is the mammalian target of rapamycin (mTOR), a kinase whose activity is very important in cellular growth processes and is inhibited by AMPK, leading to reduction of protein synthesis [31].

AMPK can be activated by exercise, hormones, cytokines and drugs [31]. Metformin activates AMPK in a dose and time dependent manner, which results in inhibition of hepatic glucose production, increased glucose uptake by muscle, inhibition of acetyl-CoA carboxylase and decreased fatty acid synthase expression in rat hepatocytes [32] and, possibly, increased glucose utilization in liver via an independent-insulin pathway [33]. The activation of AMPK by metformin seems to be independent of changes in AMP/ATP ratio [33,34], through inhibition of mitochondrial respiratory chain complex I and increase of reactive nitrogen species (RNS) [34,35]. However, another study in mice suggests that metformin can inhibit gluconeogenesis in an AMPK-independent pathway, through changes in AMP/ATP ratio [36].

Other hypotheses regarding the mechanisms of action of metformin are discussed below.

### 5.1. Incretins

The action of metformin on the incretin pathways has been proposed as another possible mechanism to explain its glucose-lowering effect. Maida et al. [37] observed that metformin acutely increased GLP-1 levels in mice without concomitant glucose administration, but didnot affect other gut peptides like peptide YY or GIP. Metformin also reduced the rate of gastric emptying and improved oral glucose tolerance, but this action was not mediated byGLP-1 [37]. No effect of metformin has been observed on DDP-4 activity [37]. Additionally, metformin induced upregulation of mRNA transcription of the GLP-1 receptor in islets of metformin-treated mice through an AMPK-independent pathway and involving PPARα [37].

### 5.2. Bile acids

Metformin alters bile acid metabolism, which is demonstrated by an increase of breath $CO^{14}$ and fecal $C^{14}$ in T2DM patients after the administration of $C^{14}$-glycocholate [38]. This action seems to be due to a decrease of bile salt absorption in the ileum as seen in animal studies [39], by a reduction of active transport, independently of Na-K ATPase [40]. This could explain gastrointestinal effects of metformin and its hypolipidemic properties and it may be involved in glucose control because bile acids activate G-protein coupled receptor TGR5, which can stimulate GLP1 release by L-cells [41]. Furthermore, Patti et al. [42] found that patients who have undergone gastric bypass have greater bile acid levels compared with overweight/obese patients and they are correlated positively with postprandial peak of GLP1 and negatively with glucose levels, so this support the idea that bile acids may stimulate GLP1.

### 5.3. Islet amyloid

Metformin also could act on glucose control through changes in islet amyloid deposits. It is known that amyloid deposits lead to a decrease in β cell mass, which is usual in T2DM. In a study with transgenic mice (expressing peptide islet amyloid), metformin, although it did not prevent amyloid formation, reduced the prevalence and severity of islet amyloid. It was found that this effect could be related to changes in body fat mass and insulin secretion [43].

Further research is clearly needed to elucidate the link between the different hypotheses regarding the mechanism of action of metformin.

## 6. Metformin and cancer

There have been reports regarding the association between T2DM and a higher risk of cancer and a worse prognosis [44–46]. This might be explained by hyperinsulinemia and insulin resistance, characteristics of T2DM, because insulin promotes growth and has mitogenic effects. Not too much is known about the role of anti-diabetic drugs in this relationship so there is an increasing interest about the anti-cancer effect of metformin, mostly after some population studies have suggested that metformin might reduce the risk of cancer in diabetic patients. Evans et al. [47] in a case–control study involving patients with newly diagnosed T2DM, found that patients on metformin had a 23% reduced risk of cancer compared to patients on sulfonylureas, even after adjusting for BMI. In another epidemiological study, involving new users of antidiabetic drugs, Bowker et al. [48] showed that the cancer-related mortality rate was significantly lower in the metformin group compared to sulfonylurea users.

Since these epidemiological reports, there have been many studies on the role of metformin in different types of cancer.

### 6.1. Population studies

It is known that hyperinsulinemia and T2DM are associated with a higher risk of breast cancer incidence and with a worse prognosis. Most of the clinical studies (Table 1) on the association of metformin with cancer are retrospective and therefore must be interpreted

with caution because of confounding factors. Nevertheless, they suggest an interesting association that merits further investigation in prospective studies.

Using a national cancer registry, Libby et al. found [49] that cancer incidence during a 10 year follow-up period was 7.3% in patients with diabetes on metformin compared to 11.6% in patients on other antidiabetic treatments. Patients on metformin had a higher median time to cancer and a lower mortality. In a different nested case–control study, metformin was also associated with reduced incidence of cancer in a cohort of more than 1000 patients [50]; after adjustments the odds ratio for metformin treatment was 0.46 (95% CI 0.25–0.85).

Metformin may also improve the prognosis of cancer. Indeed, in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study, the standardized cancer mortality ratio was 0.88 for metformin users and 1.625 for nonusers (median follow-up time: 10 years); this difference did not change after adjustment for confounding factors [51].

A small prospective pilot clinical trial [52] in 26 non-diabetic patients with aberrant crypt foci (ACF), a marker of colon carcinoma, showed that metformin treatment for 1 month reduced the number of ACF and rectal epithelial cell proliferation. This is remarkable because it points to a potential antiproliferative effect in non-diabetic patients.

This protective effect of metformin has not been observed in the ADOPT-RECORD analysis done by Home et al. [53]. Cancer occurrence was not an outcome of those prospective studies, but they analyzed the malignancies reports and concluded that metformin did not have a clear advantage over rosiglitazone and sulfonylureas. However, the number of reported cancers was so limited that the study is difficult to interpret.

On the other hand, there are studies evaluating the relation between metformin and specific cancers. Breast cancer is the one most studied in relation to metformin. Jiralerspong et al. [54] studied retrospectively the percentage of pathologic complete response (pCR) in patients with invasive breast cancer treated with neoadjuvant chemotherapy. The proportion of pCR was significantly higher in the metformin group compared to non-metformin treated patients with diabetes, without significant differences in chemotherapy doses or in insulin treatment between groups. However, there was no difference in survival. So, after adjustments, metformin use during neoadjuvant chemotherapy in invasive breast cancer was found to be an independent predictor of pCR. In another retrospective study, using data derived from the U.K.-based General Practice Research Database, long-term use of metformin (about 5 years) was associated with a lower risk of breast cancer [55], in patients with diabetes. The adjusted OR was 0.44 in metformin users compared with non-metformin users but with a small number of cases and controls being a limitation.

The use of metformin in patients with diabetes was also associated with a significant reduction in risk of pancreatic cancer (OR = 0.38; 95% CI, 0.21–0.67) in a hospital-based study, of almost 1000 patients with pancreatic adenocarcinoma [56].

Although prostate cancer is inversely associated with T2DM, hyperglycemia and hyperinsulinemia are risk factors of higher mortality. A retrospective study done by Wright and Stanford [57] suggests that Caucasian men with diabetes on metformin have a lower risk

of prostate cancer. In another study performed in more than 200 patients with diabetes and prostate cancer [58], metformin was a significant predictor of improved survival.

### 6.2. In vitro studies

Metformin can inhibit breast cancer cell growth and this effect is greater when there is overexpression of the human epidermal growth factor receptor 2 (HER2). Metformin reduces HER2 oncoprotein expression in breast cancer cells, mostly acting through AMPK and downregulation of mTOR effector p70S6K1. However, metformin may act by other mechanisms because it still has some effect when an AMPK inhibitor is used [59]. Alimova et al. [60] showed that metformin reduces proliferation and colony formation in four breast cancer lines by inducing cell cycle arrest at G1. The drug also decreases erbB2 tyrosine kinase activity, but in this study, the mTOR effect was less important.

Metformin action on breast cancer has been studied in combination with chemotherapic agents. Hirsch et al. [61] observed that the combination of metformin and doxorubicin killed stem and non-stem cancer cells and achieved a greater reduction and remission of the tumor than either drug alone. This is of interest as stem cells may be linked to relapse after chemotherapy treatment due to self-renewal capacity.

Another possible action of metformin is on the epithelial–mesenchymal transition (EMT) status, which seems to have an important role in metastatic breast cancer cells. An in vitro study [62] has shown that metformin prevents the generation of a breast cancer stem cell phenotype by repressing transcriptionally the TGFβ axis.

Metformin also can inhibit the growth of cells of triple negative (TN) breast cancer, an aggressive subtype. The drug induces G1 cell cycle arrest, but also produces apoptosis and reduces levels of epidermal growth factor receptor, frequently overexpressed in TN breast cancer. Otherwise, this growth inhibition has been observed in breast cancer cells xenografted into non-diabetic mice [63], so it is possible that metformin could be useful in both diabetic and non-diabetic conditions.

Endometrial cancer is also associated with obesity and T2DM [64]. As in breast cancer, metformin [65] inhibits growth of endometrial cancer cells and causes G1 cell cycle arrest. This is largely due to AMPK activation and at high doses it can induce apoptosis. Furthermore, metformin decreases hTERT mRNA expression in endometrial cancer cells, which is a rate-limiting determinant of telomerase activity. Moreover, treatment of sera from polycystic ovary syndrome (PCOS) women with metformin seems to decrease significantly the in vitro invasion of endometrial cancer cells [66].

Metformin has also demonstrated its anti-proliferative effect in ovarian cancer cell lines, inhibiting their growth (including chemoresistant lines) and causing G1 cell cycle arrest [67]. In these types of cells, metformin activates AMPK through LKB and leads to decreased phosphorylation of mTOR and protein–lipid synthesis. However, it has a lower impact in more aggressive cancer cells and, more interestingly, there is no a significant effect over primary ovarian cells. In another study [68] metformin was observed to induce apoptosis in ovarian cancer cells (AMPK independent manner) and induce changes in Bcl-2

proteins, increasing the relation pro-apoptotic/anti-apoptotic, suggesting that several mechanisms are involved in metformin action on cancer.

Metformin acts also on pancreatic cancer cells, blocking the crosstalk between insulin and G protein-coupled receptors (GPCR) that leads to a major GPCR-induced signaling. Metformin reduces DNA synthesis and cell proliferation induced by insulin or GPCR agonist and this action is through AMPK. Moreover, it inhibits the growth of human pancreatic cancer cells xenografted into mice [69].

### 6.3. Animal studies

Mice with colon carcinoma on a high energy diet have greater cancer growth, insulin levels and fatty acid synthase (FASN) expression. FASN is involved in fatty acids synthesis, which are an important energy substrate for cancer cells. The effect of metformin was not seen in mice on a normal diet [70].

The diet effect was also observed in mice with lung LLC1 carcinoma. These mice on a high-energy diet have a greater cancer growth compared to mice on a normal diet, this effect is almost reversed by metformin only in mice on a high energy diet, but not in mice on a normal diet. In those mice metformin also reduces high C-peptide levels and improves insulin tolerance. Metformin activates AMPK in the tumor cells, but mice on the high-energy diet have a higher phosphorylation of insulin receptor, so it may be that metformin also acts by reducing insulin levels [71]. In mice with NNK-induced lung cancer [72], oral metformin prevents growth of tumor, with a mild effect over mTOR in the lung. However, intraperitoneal administration was more effective in preventing tumorigenesis and inhibiting mTOR and it occurred without lung-AMPK activation. One explanation would be again that metformin inhibits mTOR by decreasing insulin or IGF1 levels.

Metformin, in combination with different chemotherapeutic agents, can stop the tumor growth in mice with breast cancer and delay the relapse, mostly acting on stem cells [73], a mechanism seen in in vitro studies.

Besides the effect on tumor growth, it has been reported that metformin postpones tumor development and increases the mean life span of female spontaneously hypertensive rats when it is started in early life, but does not change tumor incidence [74].

Therefore, in vitro and *in vivo* studies point to an antiproliferative effect of metformin, with an interesting interaction with diet high in energy density. Theses in vitro and animal data support the epidemiological evidence that the use of metformin is associated with a lower risk of cancer.

## 7. Conclusion

Metformin is an oral antidiabetic drug that has been used for more than 50 years. It is cost effective and very safe clinically. Studies such as the UKPDS have clearly demonstrated its glucose-lowering efficacy, mostly in overweight patients. So, with increasing prevalence of obesity and T2DM, in addition to diet and exercise, metformin seems an appropriate first-step therapy. Moreover, it is effective in diabetes prevention in high risk populations

although there are currently no guidelines for its use in this clinical setting. Its glucose-lowering effect is mostly due to its action on hepatic insulin sensitivity; its effect on bile acids, GLP-1 and amyloid deposits merit more research. There is strong epidemiological evidence, supported by in vitro and animal studies, that metformin may prevent cancer. Further clinical studies are needed to understand the mechanisms of this relationship, and whether cancer risk and/or status should be considered when prescribing antidiabetic drugs.

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**Table 1**

Summary of epidemiological studies on the association of metformin with cancer, including some possible confounding factors.

| Reference | Year | Subjects | Age (years) | Duration of diabetes (years) | Glycemic control (Hb A1c) | Other therapies | Outcomes |
|---|---|---|---|---|---|---|---|
| Libby et al. | 2009 | New users of metformin | ≥35 | | 7.9 ± 1 (metformin users)<br>7.2 ± 1.2 (comparators) | Sulfonylureas<br>Insulin | Cancer incidence in new users of metformin during 10 of years follow-up was 7.3% compared with 11.6% in patients on other treatments. This group also presented a lower mortality. |
| Li et al. | 2009 | Pancreatic cancer patients vs control subjects | The higher proportion between 61 and 70 years: 39.2% (cases) vs 33.6% (controls) | ≤2 years: 13.5% (cases) vs 3.4% control | ≤7 in 57.1% of metformin ever users vs 62% of metformin never users | Insulin secretagogues<br>Thiazolidinediones<br>Insulin | Metformin is associated with a significant reduction in risk of pancreatic cancer. |
| Jiralerspong et al. | 2009 | Invasive breast cancer patients receiving neoadjuvant chemotherapy | Median: 49 | | Median: 7.3 (metformin group) vs 7.8 (nonmetformin group) | Thiazolidinediones<br>Insulin | Metformin is an independent predictor of pathologic complete response (pCR) in diabetic patients with breast cancer receiving neoadjuvant chemotherapy. pCR in metformin group: 24%; in nonmetformin group: 8%: in nondiabetic group: 16%. |
| Wright et al. | 2009 | Prostate cancer patients vs control subjects | ≥75% of patients: 55–74 | | | Insulin<br>Sulfonylureas<br>Thiazolidinediones<br>Meglitinides | Metformin is associated with reduction in risk of prostate cancer in diabetic caucasian men. |
| Landman et al. | 2010 | T2DM patients | 67.3 ± 10.6 (metformin group) vs 68 ± 12 (nonmetformin group) | Median: 4.9 (metformin group) vs 7.1 (nonmetformin group) | 7.7 ± 1.1 (metformin group) vs 7.4 ± 1.3 (nonmetformin group) | Insulin<br>Sulfonylureas | Lower standardized mortality ratio for cancer mortality in patients on metformin, without changes after adjustment for confounder factors. |
| Bodmer et al. | 2010 | T2DM women | 67.5 ± 10.5 | ≥2: 63.3% (cases) vs 64.5% (controls) | <6.5: 22.6% (cases) vs 20.7% (controls) | Insulin<br>Sulfonylureas | Long-term use of metformin was associated with lower risk of breast cancer. The adjusted OR was 0.44 (95% CI 0.24–0.82) in metformin users compared with non-metformin users. |
| Hosono et al. | 2010 | Patients with aberrant crypt foci (no diabetic) | 69.1 ± 5.95 (metformin group) vs 64.2 ± 9.07 (controls) | | 5.8 ± 1.01 (metformin group) vs 5.4 ± 0.56 (controls) | | Metformin reduces aberrant crypt foci growth and rectal epithelial cell proliferation in non-diabetic patients, without changes in insulin levels. |
| Monami et al. | 2011 | Cancer patients vs control subjects | 68.9 ± 9.9 (cases) vs 68 ± 10 (controls) | Median: 8.4 (cases) vs 10 (controls) | | Insulin<br>Insulin secretagogues | Metformin is associated with reduced incidence of cancer. |
| He et al. | 2011 | Diabetic prostate cancer patients | 58.79%: ≤65 | | | Thiazolidinediones<br>Insulin<br>Insulin secretagogues | Metformin is a significant predictor of improved survival. |