Metformin in Cancer Treatment and Prevention

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Abstract

Patients with diabetes mellitus are at increased risk of cancer development. Metformin is a well-established, effective agent for the management of type 2 diabetes mellitus. Epidemiological studies have identified an association between metformin use and a beneficial effect on cancer prevention and treatment, which has led to increasing interest in the potential use of metformin as an anticancer agent. Basic science has provided a better understanding of the mechanism of action of metformin and the potential for metformin to modulate molecular pathways involved in cancer cell signaling and metabolism. This article outlines the link between metformin and cancer, the potential for metformin in oncology, and limitations of currently available evidence.

INTRODUCTION

T2DM: type 2 diabetes mellitus

IGF: insulin-like growth factor

Diabetes mellitus is a chronic disease leading to micro- and macrovascular complications that reduce long-term survival. The prevalence of diabetes is increasing globally and by 2030 is estimated to affect ~366 million patients worldwide (1). Even by current estimates, diabetes poses a significant economic burden. In the United States alone, the cost of diabetes management was estimated at $245 billion in 2012, a 41% increase from previous estimates in 2007 (2). Of patients with diabetes, approximately 95% have type 2 diabetes mellitus (T2DM), which develops as a result of excess caloric intake, limited physical activity, and obesity. T2DM most commonly affects older people and is characterized by insulin resistance, islet cell dysfunction, and a progressive reduction in insulin secretion. This in turn leads to reduced peripheral glucose uptake, reduced glycogen storage, and less effective glucose shunting into key metabolic pathways (3, 4). In recent years, numerous studies have reported an association between diabetes and an increased risk of developing cancer, greater than would be expected by chance alone. Epidemiological studies involving patients with T2DM have reported approximately a twofold increased risk of developing cancers of the liver, pancreas, and endometrium; increases in colorectal, kidney, bladder, and breast cancers have been reported with smaller associations (1.2- to 1.5-fold) (5). In contrast, prostate cancer has been found to occur less often in men with diabetes. Diabetic patients diagnosed with cancer also appear to have a worse prognosis. Meta-analyses have reported that diabetic patients have between a 1.3- and 1.5-fold increase in all-cause and cancer-specific mortality across certain cancer types including breast, endometrial, and colorectal cancers (6, 7). Although prostate cancer appears to be less prevalent in men with diabetes, mortality is still elevated in those who develop the disease, especially in patients with high body mass index (BMI) and hyperinsulinemia (8, 9). Evidence to support an association with rare forms of cancer is sparse.

There are several biologically plausible explanations for the association between diabetes and cancer development. Malignant transformation typically involves a process of initiation (involving multiple genetic hits) followed by promotion and progression, which stimulate cell growth and development. Patients with diabetes and cancer also share multiple common risk factors associated with initiation, including age, gender, obesity, limited physical activity, and poor dietary and lifestyle habits (10). The chronic effects of endogenous or exogenous hyperinsulinemia may also promote malignant transformation via direct or indirect mechanisms. Hyperinsulinemia may act as a growth factor by directly stimulating insulin receptors expressed on cancer cell surfaces, which are linked to downstream signaling pathways involved in cell survival and mitogenesis (11). In this respect, associations with cancers of the pancreas and liver have been reported; these organs are chronically exposed to high levels of endogenous insulin, at the time of production in the pancreas and during transportation to the liver via the portal vein. Hyperinsulinemia may also act as a growth promoter indirectly by increasing levels of insulin-like growth factors (IGFs), which can modify downstream signaling pathways involved with cell proliferation and protection from apoptotic stimuli (12). Other indirect effects of hyperinsulinemia include reducing hepatic synthesis of sex-hormone-binding globulin, leading to elevated levels of sex steroid hormones, which are associated with increased risk of cancer development (13, 14). Hyperinsulinemia can also activate chronic inflammatory processes that may trigger cancer initiation and progression (15). Additionally, cancer cells typically have high levels of glucose uptake, and in this regard hyperglycemia may create a fuel-rich environment for cancer progression.

METFORMIN

Metformin (1,1-dimethylbiguanide) is the most commonly prescribed therapy for patients with T2DM. It has an established treatment efficacy, has a good safety profile, is associated with low

cost, and is recommended in conjunction with lifestyle modification as the first-line oral therapy in T2DM (16). Metformin works by reducing insulin resistance and fasting plasma insulin levels, leading to a reduction in blood glucose concentrations without causing overt hypoglycemia. In this regard, metformin is an antihyperglycemic agent and insulin sensitizer. Although it was first introduced in the 1950s, its mechanism of action is only now becoming clear. Metformin specifically inhibits the mitochondrial respiratory chain complex 1 in a range of tissues including hepatocytes, skeletal muscle, endothelial cells, pancreatic beta cells, and neurons (17). Inhibition of mitochondrial respiratory chain complex 1 induces a transient reduction in cellular energy status, which alters the balance between adenosine triphosphate (ATP) production and consumption, leading to an increase in the intracellular ratio of adenosine monophosphate (AMP) to ATP (18). Increased levels of AMP activate AMP-activated protein kinase (AMPK) by binding to regulatory sites, causing a conformational change in the enzyme, a process dependent on the upstream actions of the serine–threonine liver kinase B1 (LKB1). AMPK is a phylogenetically conserved protein kinase that monitors cellular energy status and protects cellular functions under energy-restricted conditions. Activation of AMPK causes the cell to switch from an anabolic to a catabolic state in an attempt to restore energy balance through phosphorylation of key metabolic enzymes and activation of transcription factors that modulate gene expression (19). In turn, activated AMPK leads to inhibition of gluconeogenesis, lipogenesis, and protein synthesis while stimulating fatty acid oxidation and glucose uptake in the liver. However, metformin may also inhibit gluconeogenesis in a mechanism independent of gene expression through regulation of key enzymes involved in energy metabolism such as fructose-1,6-bisphosphatase. Furthermore, although the primary target for metformin is thought to be the mitochondrial respiratory chain complex 1, a separate mechanism of action may also exist because metformin has also been shown to influence the metabolism of erythrocytes, which characteristically lack mitochondria (17). Further research into the exact mechanism of action of metformin is ongoing.

AMPK: adenosine monophosphate-activated protein kinase

LKB1: serine-threonine liver kinase B1

ALTERED CANCER METABOLISM

Under typical aerobic conditions, normal cells generate energy in the form of ATP primarily through mitochondrial oxidative phosphorylation. However, metabolism in most cancer cells is altered so that cells generate large amounts of lactate regardless of the availability of oxygen, a process called aerobic glycolysis. This phenomenon is termed the Warburg effect and was named after Otto Warburg, who first described the altered metabolism of glucose by cancer cells in 1924 (20). Although aerobic glycolysis is less efficient at generating ATP than oxidative phosphorylation, it is thought that cancer cells switch to aerobic glycolysis to facilitate the uptake and use of nutrients such as nucleotides, amino acids, and lipids in order to support cell growth and proliferation. In this regard, several signaling pathways involved in cell proliferation constitutively activate the uptake and metabolism of nutrients that fuel cell growth and survival. Oncogenes such as Myc and nuclear factor kappa B (NF-κB), as well as several tyrosine kinase growth factor receptors such as insulin-like growth factor 1 (IGF-1) and human epidermal growth factor receptor 2 (HER-2), activate proliferating pathways including phosphoinositide 3–kinase (PI_3K) and mammalian target of rapamycin (mTOR), leading to the transcription of genes involved in glycolysis (21). Activation of these signaling pathways enhances glucose uptake and negatively regulates flux through glycolysis, allowing glycolytic intermediates to become available for macromolecular synthesis (20). In contrast, AMPK can inhibit cell proliferation and has been referred to as a metabolic tumor suppressor. Several tumor suppressor proteins lie both up- and downstream of AMPK, including p53, LKB1, and tuberous sclerosis complex 2 (TSC2). AMPK activates TSC2 to form a complex with TSC1, which regulates the activity of mTOR complex 1 (mTORC1), which in turn regulates

protein translation important for cell growth. In this respect, loss of AMPK activity has been shown to promote the development of lymphoma in in vivo animal models (22). LKB1/AMPK activation in response to cell stress reduces metabolic flux through glycolysis, which may be an adaptive response to inhibit proliferative metabolism during episodes of reduced energy availability or oxidative stress (23). Although AMPK appears to be a key enzyme, cancer cells rarely display mutations in AMPK. Mutations tend to affect upstream and downstream targets, such as LKB1. Mutations in LKB1 are responsible for the Peutz-Jeghers syndrome, a rare autosomal dominant condition characterized by benign and malignant tumors and mucocutaneous pigmentation (24).

MECHANISM OF ACTION OF METFORMIN IN CANCER

Several biologically plausible mechanisms also exist to explain an association between metformin and reduced cancer development and progression (**Figure 1**). These mechanisms focus largely on inhibiting growth stimuli and metabolic processes within cancer cells and can be divided into insulin-dependent and -independent mechanisms that alter cancer cell growth. Insulin and IGF-1 are both potential growth factors capable of stimulating cell survival and mitogenesis,

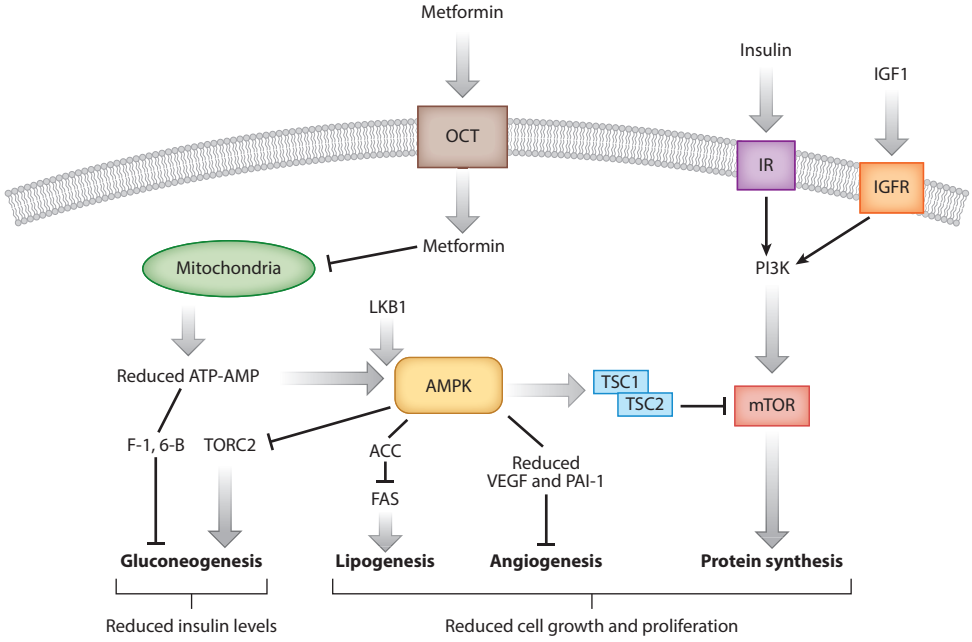

Figure 1

Potential molecular mechanism of action of metformin in cancer. After uptake by the organic cation transporter (OCT), metformin causes a reduction in ATP via inhibition of the mitochondrial respiratory chain complex 1 leading to activation of adenosine monophosphate-activated protein kinase (AMPK). Activated AMPK may disrupt gene expression involved in gluconeogenesis, lipogenesis, protein synthesis and potentially angiogenesis. Abbreviations: ACC, acetyl-CoA carboxylase; F-1,6-B, fructose-1,6-bisphosphatase; FAS, fatty acid synthase; IGF, insulin-like growth factor; LKB1, serine-threonine liver kinase B1; mTOR, mammalian target of rapamycin; PAI-1, plasminogen-activator inhibitor-1; PI3K, phosphoinositide 3-kinase; TORC2, transducer of regulated CREB-binding protein 2; TSC2, tuberous sclerosis 2; VEGF, vascular endothelial growth factor.

whose receptors are expressed on many cancer cells including cancers of the breast, liver, colon, pancreas, and skin (12). It is therefore possible that treatment with metformin lowers serum levels of insulin and IGF-1, thus reducing the stimulus for growth. Reductions in insulin and IGF-1 induced by calorie restriction have been shown to reduce incidence of cancer in in vivo animal models (25). Also, in vitro studies have shown that under certain circumstances the direct withdrawal of glucose may induce cell death in a similar fashion to the withdrawal of growth factors (26). Given the potential importance of the Warburg effect in cancer metabolism, a glucose-rich environment could provide favorable conditions for aerobic glycolysis. Treatment with metformin would therefore reduce hyperglycemia and any associated growth advantage in susceptible tumors.

Several plausible insulin-independent mechanisms also exist. First, activation of LKB1/AMPK signaling by metformin could inhibit aerobic glycolysis in cells containing functional LKB1/AMPK pathways. Metformin could also induce tumor cell death in cells lacking functional LKB1/AMPK pathways through the reduction in ATP levels, making susceptible cells unable to respond to energy stress (27). The anticancer effects of metformin may also be mediated through regulation of fatty acid synthesis dependent on AMPK activation. Fatty acid synthase (FAS) is a key enzyme in fatty acid biosynthesis, is associated with an increased risk of malignant transformation, and is constitutively overexpressed by a number of cancer cells, including breast and colon (28). AMPK activation has been shown to reduce FAS expression and subsequent growth of prostate cancer cells in vitro (29). Second, metformin may influence chronic inflammation, which can be an important factor in the initiation and promotion of carcinogenesis. Obese subjects characteristically develop a chronic proinflammatory environment with increased infiltration of immune cytokines such as leptin, adiponectin, interleukin 1 beta (IL-1β), IL-6, plasminogen-activator inhibitor-1 (PAI-1), and tumor necrosis factor alpha (TNFα), which are associated with cancer proliferation and progression (30, 31). AMPK activation appears to inhibit the synthesis of proinflammatory cytokines in a variety of cell types, including macrophages and adipocytes. This suggests that metformin could potentially target proinflammatory cytokines within the tumor microenvironment, inhibiting growth in susceptible cancers (32). Last, metformin may have important effects in limiting tumor growth and metastasis by inhibiting endothelial cell migration and angiogenesis via AMPK-dependent reductions in growth factors including vascular endothelial growth factor and PAI-1 (33).

METFORMIN AND CANCER TREATMENT

Cancer treatment may attempt to cure, reduce tumor growth, relieve symptoms, improve the efficacy of adjuvant therapy, or prevent recurrence. Numerous in vitro and in vivo animal studies have demonstrated growth-inhibiting effects of metformin in breast, endometrial, lung, liver, gastric, and medullary thyroid cancer cell lines (34). Antiproliferative effects have also been demonstrated in several hemopoietic cancer cells, including acute myeloid and promyelocytic leukemia cells. These effects are thought to stem from growth inhibition via cell cycle arrest and from increased cytotoxicity via the induction of apoptosis. Several laboratory studies have demonstrated an increased sensitivity to chemotherapy in a variety of cancer cell lines treated with metformin. Studies of the effects of cisplatin, carboplatin, doxorubicin, and paclitaxel on breast, endometrial, and ovarian cancer cell lines and xenograft experiments have suggested a role for metformin as adjuvant therapy (35–37). In vitro evidence suggests that metformin may also protect from several important side effects of chemotherapy, such as cisplatin-induced ototoxicity and doxorubicin-induced cardiotoxicity (38, 39).

Several cohort studies using patient data from primary and secondary care have reported an association between metformin and improved cancer survival following adjusted analysis. These

studies commonly apply survival analysis and report the hazard ratio (HR), where a HR of 0.6 is equivalent to a 40% reduction in the hazard of developing the outcome of interest between two groups. In a prospective cohort study involving 1,353 T2DM patients from the Netherlands, metformin use was associated with a significant 57% reduction in cancer-specific mortality (40). A large retrospective study from Canada involving 10,309 new users of metformin or sulfonylureas reported a significant 20% reduction in cancer mortality in metformin users compared with sulfonylurea monotherapy users (41). A subsequent study from the United Kingdom also reported a 15% reduction in overall mortality following cancer diagnosis among metformin-treated patients (42). A large meta-analysis of studies investigating the association between metformin use and cancer-specific mortality involving 28,671 patients reported a significant overall 35% reduction in cancer mortality among metformin users from observational studies, but no significant reductions in cancer mortality were seen among metformin users from randomized controlled trials (43).

Breast Cancer

Pathologic complete response (pCR) after neoadjuvant treatment is defined as the absence of tumor cells in the breast at surgical resection and is considered an important predictor of reduced long-term breast cancer mortality. In a US study of diabetic patients, metformin exposure was associated with a significantly higher rate of pCR to neoadjuvant chemotherapy for invasive breast cancer compared to either diabetic patients without metformin or nondiabetic patients (24% versus 8% versus 16%). Metformin exposure was also an independent predictor of pCR in addition to other well-established predictors of pCR, such as HER-2 status and neoadjuvant taxane use (44). In a subsequent smaller study restricted to patients with triple receptor–negative breast cancers (which do not express estrogen or progesterone receptors, nor HER2 cell-surface receptors, and are therefore unlikely to respond to hormonal or HER2-targeted therapies), overall survival in metformin users was not significantly improved, although a nonsignificant trend toward a lower risk of distant metastasis was noted (45). Although similar nonsignificant differences in breast cancer survival among patients exposed to metformin have been reported, other studies show significant reductions in recurrence. In a study involving 1,031 diabetic breast cancer patients, users of metformin had significantly better five-year breast cancer survival rates compared to other patients (42, 46).

Liver Cancer

Relatively few studies investigating the association of metformin with liver cancer prognosis have been conducted. In one small study involving 135 patients, diabetic patients undergoing radiofrequency ablation for early-stage liver cancer had worse survival rates compared to nondiabetic patients (five-year survival 41.3% versus 64.7%). However, diabetic patients exposed to metformin had a significantly improved prognosis, similar to that seen in nondiabetic patients (five-year survival 60.5% versus 64.7%) (47). Similar associations have also been reported in a larger cohort study involving 1,460 patients with liver cancer, where metformin exposure at the time of liver cancer diagnosis was associated with a significant 53% reduction in mortality (42).

Ovarian/Endometrial Cancer

A US study involving 341 patients with invasive ovarian cancer reported a significantly better overall five-year survival rate for diabetic patients exposed to metformin compared to other diabetic and nondiabetic patients (63%, 23%, and 37%, respectively). Following adjusted analysis,

metformin exposure was associated with a 68% reduction in disease recurrence and a nonsignificant reduction in cancer-specific mortality (48). Similar findings were reported in a case-control study, in which women with ovarian cancer exposed to metformin had a five-year disease-specific survival of 73% compared to only 44% in unexposed women (49). In this analysis, metformin use was also an independent predictor of survival after adjusting for disease stage, grade, histology, chemotherapy, surgical cytoreduction, and BMI. Although an association between metformin exposure and improved survival with endometrial cancer has been reported, this survival benefit was limited to the nonendometrioid subtype, suggesting that response to metformin may differ according to histological tumor subtype (50). Similar reductions in mortality among metformin users following a diagnosis of ovarian and endometrial carcinoma have also been reported in larger cohort studies (42).

Other Cancers

Survival advantages in diabetic patients exposed to metformin have been reported for several other cancer types, including colorectal and pancreatic, where metformin exposure was associated with a 40% and a 32% improvement in overall survival, respectively (51, 52). In addition, metformin exposure has been associated with a dose-dependent increase in response to neoadjuvant chemoradiation and an increased rate of pCR in esophageal adenocarcinoma (pCR 34.5% for diabetic metformin users versus 4.8% for other diabetics and 19.6% for nondiabetic patients) (53). Metformin use has also been associated with better progression-free survival in diabetic patients with advanced non–small cell lung cancer (53, 54). Despite these positive associations, not all studies have demonstrated consistent benefits with metformin upon site-specific analysis (42). In many instances, users of sulfonylureas or insulin do appear to have significantly worse cancer-specific survival compared to either metformin users or nondiabetic patients (40, 42, 46).

Clinical Trials of Metformin in Cancer Treatment

Metformin has been evaluated in several presurgical clinical trials of breast cancer involving nondiabetic women. A total of 47 women with core biopsy at breast cancer diagnosis were randomized to a controlled study of metformin until the time of surgery. Compared to control, metformin-treated patients had significant reductions in cell staining for Ki67 (an independent prognostic marker for disease-free and overall survival in breast cancer), altered tumor necrosis factor receptor 1 signaling, and reduced expression of p53, BRCA1, and cell cycle pathways (55). In a similar study, 39 women with operable breast cancer were treated with metformin 500 mg three times daily after biopsy until surgery. Invasive tumor tissue samples from metformin users had significant reductions in Ki67 staining and an increase in the number of cells undergoing apoptosis (56). In a larger study, 200 nondiabetic women with operable breast cancer were randomly allocated to metformin 850 mg twice daily or placebo following biopsy. Interestingly, metformin caused significant reductions in Ki67 cell staining but only in women with insulin resistance [as assessed by homeostasis model assessment (HOMA) index >2.8] (57).

One pilot study evaluated metformin exposure on rectal aberrant crypt foci, an endoscopic surrogate marker for colorectal cancer. In this study, 26 nondiabetic patients with aberrant crypt foci were randomly allocated to metformin 250 mg daily for one month, at which point repeat colonoscopy was performed. Compared to control, metformin users had a significant reduction in the mean number of aberrant crypt foci and proliferative activity (as assessed by the proliferating cell nuclear antigen index), while apoptotic activity remained unaltered (58). These studies provide evidence for a potential antiproliferative effect of metformin in patients with breast cancer and

colorectal cancer, and also suggest that response to metformin may depend on the degree of underlying insulin resistance.

METFORMIN AND CANCER PREVENTION

Observational Studies of Cancer Prevention

The first observational study linking metformin to the prevention of cancer was a case-control study involving 923 T2DM patients from the United Kingdom. It found that metformin use was associated with a 23% reduction in the risk of developing cancer (59). Since then, there has been a rapid increase in the number of observational studies investigating the association between metformin use and risk of cancer development, resulting in several meta-analyses attempting to synthesize the emerging evidence. One such meta-analysis involving 18 observational studies and 561,836 patients reported that metformin use was associated with an overall 27% reduction in the risk of developing any malignancy (43). Consistent positive associations were reported in a separate meta-analysis whereby observational studies were meta-analyzed according to study design, with both cohort and case-control studies producing significant results in favor of metformin (60). Observational evidence for the putative effects of metformin also extends to several site-specific cancers including liver, colorectal, pancreatic, stomach, and esophageal cancers (43). In contrast, no strong associations between metformin use and the risk of developing breast, prostate, lung, or ovarian cancer have been found (43, 61).

Clinical Trials of Cancer Prevention

Clinical trial evidence regarding the relationship between metformin use and risk of cancer development comes mainly from the reanalysis of individual patient data from ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes), which were large randomized controlled clinical trials assessing the efficacy and safety of metformin compared to sulfonylureas and rosiglitazone. ADOPT randomized 1,454 patients to metformin with a total of 4,906 person-years of exposure. The incidence of malignancy among metformin users was 1.03 per 100 person-years, which was not significantly different from the incidence among rosiglitazone or glibenclamide users (62). RECORD randomized 1,122 patients to metformin with a total of 6,126 person-years of exposure, and the proportion of patients developing malignancies was similar among metformin and rosiglitazone users (6.1% versus 5.1%). Furthermore, meta-analyses of clinical trials, which are heavily weighted by the above two studies, have consistently reported no significant difference in the risk of developing cancer in metformin users compared to nonusers, in stark contrast to many observational studies (43, 60).

LIMITATIONS OF CURRENT EVIDENCE

Laboratory Studies

It is generally accepted that not all in vitro and in vivo work with animal models translates into clinical outcomes in humans. Although there appears to be considerable laboratory evidence to support the role of metformin in cancer treatment, in many instances the concentrations of metformin used in in vitro studies are well above expected therapeutic concentrations in humans (34). Additionally, not all cancer types or subtypes may respond to metformin in the same way.

Metformin has been reported to inhibit the anticancer activity of cisplatin in several different cell lines in vitro through an AMPK-independent process, suggesting the need to consider unintended effects associated with metformin use as neoadjuvant therapy in some cancer patients (63).

Observational Studies

Evidence from well-conducted randomized controlled clinical trials is typically considered superior to that from observational studies because observational studies can be subject to bias as a result of problems with study design and unknown or unmeasured confounders. Several observational studies evaluating the association between metformin exposure and the risk of cancer development and survival have been criticized as suffering from time-related biases, including immortal-time bias, time-window bias, and time-lag bias (64).

In observational studies, immortal time is a period of time in which the outcome of interest could not occur and is often related to the chosen definition of exposure. Immortal-time bias occurs when patients unexposed to the drug of interest are misclassified as being exposed and this person-time is then included in the analysis. For example, a cohort study that defines groups by ever being exposed to metformin and includes the person-time between cohort entry and the first metformin prescription in the analysis would suffer from immortal-time bias. By definition, patients would be cancer-free during this person-time but would be analyzed as if being exposed to metformin, thus underestimating the incidence of cancer in the metformin-exposed group. Time-window bias may occur in case-control studies if controls have longer periods of follow-up or treatment and therefore a greater possibility of receiving the exposure of interest. Time-lag bias may occur when comparing medicines used at different stages of disease, which can introduce confounding by indication as the intended treatment may be related to the risk of future health outcomes. For example, when considering a comparison between metformin (a first-line agent) and sulfonylureas (a second-line agent), it is possible that cancer may be diagnosed more often during exposure to sulfonylureas owing to the long latency period. Common to all of these biases is the misclassification of exposure, which may overestimate a potentially beneficial effect of a drug or artificially create one when no such benefit exists. It is difficult to know the full impact of these biases on results from existing observational studies, as reanalysis appears uncommon and results have been embedded within existing meta-analyses without proper evaluation.

In response to these concerns, several observational studies designed to avoid these time-related biases have been conducted. In these studies of patients with T2DM, metformin exposure was not associated with a significantly reduced risk of developing prostate, colorectal, bladder and lung cancers (65–68). In summary, some observational studies may be insufficiently powered to detect significant associations and others may inadequately deal with time-varying changes in drug exposure, differences in disease severity or differences in underlying biological phenotype such as the degree of insulin resistance.

FUTURE DIRECTIONS

Despite limitations, the combined data from laboratory studies, observational studies, and presurgical trials support the conduct of controlled clinical trials of metformin as adjuvant cancer treatment in those cancers with the strongest evidence base. One such clinical trial currently in follow-up is a randomized controlled trial evaluating adjuvant therapy with metformin in more than 4,000 women undergoing surgical treatment for invasive breast cancer (69). The primary outcome of this trial is invasive disease–free survival with secondary outcomes relating to overall survival, changes in BMI, new diagnoses of diabetes, cardiovascular hospitalizations, and metabolic parameters such

as insulin resistance. Another clinical trial currently under way aims to determine whether adjuvant therapy with metformin improves disease-free survival in women with advanced ovarian, primary peritoneal, and fallopian tube cancer (70). The results from both these trials due for completion in 2016 are likely to be important in determining whether further clinical trials of adjuvant therapy with metformin in cancer treatment are warranted.

The justification for clinical trials of metformin in cancer prevention is less certain, given the inconsistencies in available evidence, the long latency periods involved, and the significant costs and number of patients that would be required to confirm its benefit. It would perhaps seem prudent to await the results of clinical trials in cancer treatment and to conduct further research in an attempt to characterize patient phenotypes more likely to respond to metformin, such as those with high levels of insulin resistance at baseline. Clinical trials of metformin in cancer prevention would be more feasible in higher-risk populations, such as patients with *BRCA1* and *BRCA2* gene mutations who have significantly elevated lifetime risks of breast and ovarian cancers (73% and 41%, respectively, by age 70 years) (71). Other high-risk groups include patients with premalignant conditions such as colorectal polyps or Barrett's esophagus. Indeed, a multicenter double-blind placebo-controlled randomized trial of metformin in the prevention of colorectal polyps in nondiabetic patients is currently under way (72). If proven effective, metformin will be an attractive anticancer agent because of its safety, tolerability, and widespread availability, but further investigation into the effects of metformin are required to properly assess its potential in oncology.

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