Mysterious Metformin

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Patients with diabetes are at a higher risk for cancer. Numerous meta-analyses have demonstrated that they have a higher incidence of cancers of the liver [1], pancreas [2], endometrium [3], breast [4], colon [5], and bladder [6], and non-Hodgkin’s lymphoma [7], with a relative risk in the range of 1.2–2.5. Potential mechanisms to explain this greater risk include the mitogenic effects of insulin (baseline hyperinsulinemia, exogenous insulin) and underlying metabolic abnormalities such as increased oxidative stress, hyperglycemia, hyperlipidemia, and obesity [8]. When diabetic patients get cancer, the prognosis is unfavorable compared with nondiabetics. A recent meta-analysis found a 1.4-fold higher risk for all-cause mortality for diabetic subjects [9].

A surprising finding in recent epidemiological studies was that metformin (Fig. 1) lowers the risk for several types of cancer in type II diabetics (Table 1). A case–control study of patients in Scotland showed that metformin usage decreased the risk for any cancer diagnosis [10]. The authors identified a dose–response relationship between higher metformin use, duration of use, number of prescriptions, and amount dispensed and lower rates of cancer [10]. A follow-up cohort study among new metformin users with type II diabetes over a 10-year period revealed a 37% lower adjusted incidence of cancer, with one less cancer per 23 patients treated with metformin [11, 12]. Compared with sulfonylureas and insulin, metformin was linked to either a lower cancer incidence or lower mortality in two studies, although sulfonylurea-treated patients were older than metformin-treated subjects in both studies [13, 14]. The apparent protective effect of metformin has been demonstrated in pancreatic and prostate cancer as well [15, 16].

It remains unclear whether metformin exerts an actual protective effect, blocks a potential mitogenic property of insulin, or is primarily used in patients with less severe diabetes. Controversy erupted recently over claims that insulin glargine may raise the risk for cancer over that seen with other insulins [17, 18] and metformin [13]. These reports were criticized as methodologically flawed [19], and other studies failed to show a specific greater risk with insulin glargine than with other insulins [20, 21]. (For a detailed cogent analysis of this controversy, see Ehninger and Schmidt [22] and the perceptive commentary by de Miguel-Yanes and Meigs [23].)

Not only have epidemiological studies indicated a cancer-preventive effect of metformin, but there has emerged intriguing evidence that metformin may enhance chemotherapy for established tumors. In a study of diabetic, early-stage breast cancer patients treated with neoadjuvant chemotherapy, metformin users had a higher pathologic...
complete response rate, defined as the absence of invasive carcinoma of the breast or axillary lymph nodes at the time of surgery [22]. The idea that metformin may somehow protect against cancer has led to initiation of ongoing clinical trials of metformin in breast cancer treatment and prevention [25, 26].

How might metformin exert its mysterious effects in both diabetes and cancer? In 2001, Zhou and colleagues found that metformin indirectly activates AMP kinase, a key sensor of the balance of cellular ATP and AMP concentrations [27]; this activation of AMP kinase possibly results from the drug’s partial inhibition of the mitochondrial respiratory chain (Fig. 1) [28]. Once activated, AMP kinase phosphorylates the transcriptional activator TorC2, blocking its nuclear translocation and inhibiting expression of genes involved in gluconeogenesis [29]. This mechanism is thought to underlie the ability of metformin to lower glucose and insulin levels, explaining its therapeutic effect in diabetes [30]. There is evidence that AMP kinase may play a role in tumor suppression. AMP kinase is activated by the product of the Peutz-Jegher tumor suppressor gene LKB1. Loss of LKB1 function is a frequent finding in lung adenocarcinoma and squamous cell carcinomas [31]. Mice deficient in hepatic LKB1 develop hyperglycemia and are resistant to the glucose-lowering effects of metformin [32].

![Figure 1. Mechanism of metformin action in diabetes. Metformin is thought to partially inhibit oxidative phosphorylation, altering the ATP–AMP ratio [28]. This activates AMP kinase (AMPK), which phosphorylates TorC2, blocking its nuclear translocation and transcription of genes involved in gluconeogenesis [29]. The kinase and tumor suppressor LKB1 is essential for the activity of AMPK [32].](image)

**Table 1.** Studies showing metformin reduces cancer risk in type II diabetics

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Subjects</th>
<th>Findings</th>
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<tr>
<td>Case–control [10]</td>
<td>11,876 patients newly diagnosed with type II diabetes in Scotland in 1993–2001</td>
<td>Patients who took metformin during the 8-year study period had a lower risk for hospital admissions for cancer (adjusted odds ratio, 0.77). A dose–response effect was observed for duration of metformin treatment and number of prescriptions/total amount of metformin dispensed.</td>
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<td>Observational cohort [12]</td>
<td>4,085 type II diabetics in Scotland treated with metformin compared with diabetic comparators who never used the drug in 1994–2003</td>
<td>Cancer diagnosed in 7.3% of metformin users versus 11.6% of controls, adjusted for age, body mass index, smoking status, A1c.</td>
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<td>Case–control [15]</td>
<td>973 patients with pancreatic adenocarcinoma and 863 controls in Texas in 2004–2008</td>
<td>Diabetic patients treated with metformin had a lower risk for pancreatic cancer (odds ratio, 0.38).</td>
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<tr>
<td>Case–control [16]</td>
<td>1,001 prostate cancer patients and 942 controls in Washington state in 2002–2005</td>
<td>Metformin use was associated with a 44% lower risk for prostate cancer, although the adjusted odds ratio was 0.56 with a 95% confidence interval of 0.32–1.0.</td>
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<td>Retrospective cohort [14]</td>
<td>10,309 patients treated with metformin or sulfonylureas in 1991–1996 in Saskatchewan</td>
<td>Sulfonylurea and insulin users had a higher cancer mortality (hazard ratio, 1.3 and 1.9, respectively). Confounding factors include insulin use associated with more severe disease.</td>
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<tr>
<td>Retrospective cohort [24]</td>
<td>2,529 patients with early-stage breast cancer receiving neoadjuvant chemotherapy in 1990–2007</td>
<td>Metformin users had a 24% pathologic complete response rate, compared with 8% of diabetics not on metformin. No differences in disease recurrence or overall survival were observed.</td>
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<tr>
<td>Retrospective cohort [13]</td>
<td>62,809 diabetics in the U.K. treated with metformin, sulfonylureas, and insulin</td>
<td>Metformin decreased the risk for colon or pancreatic cancer but not breast or prostate cancer. The combination of metformin with insulin reversed the higher rates of malignancy.</td>
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The involvement of a tumor suppressor pathway as a target for metformin’s action in glucose homeostasis prompted studies of possible effects in tumor cells and animal cancer models. Metformin exerts in vitro inhibition of the proliferation of prostate [33], ovarian [34], and breast [35–37] cancer cells. This inhibitory effect is seen, however, at concentrations (≥100–500 μM) that are at least tenfold higher than the peak plasma concentration attained with typical dosing in diabetics (~10 μM) [38]. Mouse xenograft models demonstrate in vivo antitumor effects of metformin against pancreatic [39], prostate [33], and p53 mutant colon [40] cancers. Metformin delays the onset of tumors in mice deficient in the PTEN tumor suppressor [41] and prevents pancreatic cancer in hamsters fed a high-fat diet and exposed to a pancreatic carcinogen [42].

The discovery that metformin selectively kills cancer stem cells adds further interest and may explain its antineoplastic properties. Hirsch and colleagues genetically manipulated human breast epithelial cells to enrich for stem cells, and tested these along with three distinct breast tumor cell lines [43]. Using flow cytometry to track the effects of metformin, researchers found that the drug is selectively toxic to cancer stem cells. Whereas the lowest concentration of metformin tested in vitro on stem cells (100 μM) is considerably less than the concentration used in other in vitro studies, it is still at least tenfold above the steady-state concentrations achieved with typical dosing in diabetics (~10 μM) [38]. To test metformin’s action in vivo, mice were implanted with transformed mammary epithelial cells and treated with three cycles of metformin and with the anthracycline doxorubicin. When combined with doxorubicin, metformin wiped out tumors and prevented recurrence. Metformin alone had no effect, and doxorubicin as a single agent initially shrank tumors but they later regrew. Virtually no cancer stem cells were recovered immediately after treatment, and the complete response was sustained for nearly 2 months. Further studies will delineate whether the AMP kinase pathway is important in cancer stem cells, and if the synergistic effect of metformin and anthracyclines is generalized to other types of cancer and to its combination with other drugs.

Metformin is a relative of isoamylene guanidine, the active ingredient in the French lilac (Galega officinalis), used for centuries to treat polyuria in diabetics [44]. The related compounds phenformin and buformin were withdrawn from clinical use in the 1970s after association with lactic acidosis [45], which occurs much less frequently with metformin. The risk–benefit ratio of phenformin or buformin in treating malignancy supports resurrecting these drugs and congeners for preclinical studies on the AMP kinase pathway and cancer stem cells. Metformin is also used to treat polycystic ovary syndrome, by increasing insulin sensitivity [46], and it will be interesting to follow the rate of malignancy in this treatment group. If metformin ultimately helps cancer patients, it will join drugs such as thalidomide, retinoic acid, and arsenic, which have unique, if not exotic, mechanisms of action and were first used elsewhere in medicine but found their way into the arsenal of anticancer drugs.

**AUTHOR CONTRIBUTIONS**

Conception/Design: Curtis R. Chong, Bruce A. Chabner  
Manuscript writing: Curtis R. Chong, Bruce A. Chabner  
Final approval of manuscript: Curtis R. Chong

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