Life Extension Magazine November 2010

ON THE COVER

The Drug Virtually Everyone Should Ask their Doctor About

By Julius Goepp, MD

With each passing year, fresh scientific evidence emerges to vindicate **Life Extension®'s** contention that aging humans can derive enormous benefit from an antidiabetic drug called **metformin.**

In 2010 alone, scientists at top-ranked institutions made landmark discoveries that *broaden* its use to combat degenerative disease.

The ability of metformin to help facilitate **weight loss** has long been known. What few doctors understand are the unique mechanisms by which metformin can prevent and even help treat certain **cancers.**

In a remarkable finding, a team of Swiss researchers found that diabetic women on a long-term metformin regimen (5 years or more) experienced a **56%** reduction in **breast cancer** risk![1] It also slashed **pancreatic cancer** rates by **62%** in diabetics and may cut lung cancer rates in smokers.[2,3]

In this article, a novel link between **impaired glucose control** and **cancer** is detailed. You will discover the growing list of cancers metformin may effectively combat, including those of the **colon, uterus,** and **prostate.** You will also learn of a striking connection between the anti-cancer mechanisms of **metformin** and **calorie restriction!**

WHY METFORMIN SHOULD BE VIEWED DIFFERENTLY THAN OTHER DRUGS

Many Life Extension members like to brag that they do not need to take any prescription drugs. Given the lethal side effects posed by so many FDA-approved medications, avoiding them whenever possible makes sense.

Metformin is an exception! Its broad-spectrum anti-aging properties make it a drug that most longevity enthusiasts should seriously consider asking their doctors about.

Since it long ago came off patent, metformin is a super-low cost generic that everyone can afford.

METFORMIN WAS ORIGINALLY A BOTANICAL COMPOUND

Although it is sold as a prescription drug today, metformin has a long history as a botanical compound. It was originally derived from the French lilac (*Gallega officianalis*), which has had a place in folk medicine for hundreds of years.[4,5]

After decades of neglect in the 20th century, metformin was rediscovered during the acceleration of the global epidemics of obesity and type 2 diabetes. Metformin was approved by the FDA as a treatment for type 2 diabetes in 1994, and it became the most widely prescribed drug for this disease.[6]

Beginning around 2002, a series of epidemiological studies revealed a remarkable trend: diabetic patients taking metformin were less likely to die compared to diabetics using other forms of therapy, including other oral glucose-lowering drugs or insulin.[7,8] The earlier studies also demonstrated specific benefits in protecting against cardiovascular diseases.[9,10] By 2005, evidence from large, population-based studies was becoming clear: people taking metformin for diabetes were significantly and reliably protected against the increased cancer risk posed by the diabetes itself.[2,11-15] Why should this be? The answer lies in a hidden relationship between elevated blood glucose and cancer development.

Diabetics are predisposed to a terrifyingly broad range of cancers of the liver, pancreas, colon, breast, endometrium (uterine lining), kidney, and possibly other tissues.[16-18] Scientists theorized that if ways to *reduce* chronic blood sugar elevations and other molecular consequences associated with weight gain were discovered, this would have a powerful impact in interrupting some of the pathways that lead to cancer. Metformin, it turns out, acts in a multitargeted fashion to accomplish precisely those effects.[18,19]

The simplest way to understand metformin's role in cancer prevention is to recognize that it is a powerful calorie restriction-mimicking drug.[20] It acts to essentially "fool" the body into "believing" that it is in a calorie-restricted state, thereby switching on the same protective mechanisms that arise from calorie restriction itself.

Let's now see how all this biochemistry translates to genuine anti-cancer action.

BREAST CANCER

Some of metformin's most compelling effects are in cancers of the reproductive system because it blocks the enzyme called aromatase, which can stimulate estrogen-dependent cancer growth.[21] Breast cancer is the most common malignancy diagnosed in women.[22] Fortunately, most varieties of breast cancer are proving to be especially susceptible to metformin prevention in the laboratory, and to metformin treatment in human patients, as shown by studies that have emerged over just the past two years.[23]

Metformin suppresses a specific cancer-inducing protein (human epidermal growth factor receptor 2, or HER2)[24] that dramatically increases the risk of breast cancer.[25] By suppressing HER2, which can stop cancers from developing in the first place, metformin halts cancer cells' reproductive cycle, preventing them from growing once they have developed.[26]

Via a different set of mechanisms, metformin selectively targets cancer stem cells, cells that resist chemotherapy drugs and can regenerate and cause relapse of the disease.[27] In live animal studies, metformin suppressed breast cancers, especially in animals on a high-calorie diet.[20] In a dramatic 2010 study, metformin extended the life span of mice with HER2-positive breast cancers, delayed the onset of tumor development, and inhibited the growth of implanted tumors.[19]

The combination of all these effects means that metformin is effective against many different types of breast cancers, including those that are estrogen receptor positive and negative, and those that express both normal and excessive amounts of HER2.[28] Indeed, data appeared in 2010 that long-term (greater than 5-year) *metformin use by humans is associated with a substantial (56%) reduction in risk for developing breast cancer* as compared with no use of metformin.[1]

Human trials have already demonstrated that diabetic patients with breast cancer who receive metformin plus chemotherapy have a higher rate of complete remission than do those not taking metformin. Complete remission occurred in 24% of diabetic patients taking metformin, 8% of diabetic patients not taking metformin, and 16% of non-diabetic patients not taking metformin.[29] And a 2009 study showed that metformin induced unique, multitargeted responses in so-called "triple-negative" breast cancer cells, which represent some of the most difficult-to-treat forms of the malignancy.[30]

All of these findings speak to metformin's tremendous potential as a true breast cancer chemopreventive agent—one that can and should be used long before any sign of cancer has appeared. Scientists from around the world believe that the time has come to leverage these effects in breast cancer chemoprevention and treatment.[22,23,31,32]

WHAT YOU NEED TO KNOW: METFORMIN

- Close links between diabetes and cancer have been recognized for more than a century, but the causative mechanisms have only recently been clarified.
- Diabetes and even undetected chronic elevations in blood sugar (insulin resistance) lead to tissue damage and increased insulin levels which can initiate and promote cancer in many tissues.
- Metformin is a safe and widely-prescribed drug approved for use in type 2 diabetes; it is also a powerful calorie restriction-mimicking drug.
- Metformin's calorie restriction-like actions include activation of a powerful and ubiquitous metabolic sensor called AMPK.
- Activation of AMPK and its consequences subject cancer cells to unique metabolic stresses not experienced by healthy tissues, promoting death (and even preventing development) of cancer cells early in the cancer development process.
- Metformin also independently inhibits an age-accelerating complex called mTOR that is implicated in cancer development.
- While existing mTOR-inhibiting drugs are highly toxic, metformin inhibits mTOR without discernible side effects.
- Metformin's other multitargeted anticancer effects combine with AMPK activation to suppress cancer throughout the

body.

- Metformin-induced protection has been demonstrated in cancers of the breast, endometrium, prostate, pancreas and colon, and will likely prove effective in virtually all cancers.
- A serious calorie restriction-mimetic regimen should include metformin along with other proven nutraceuticals to optimize protection against cancers throughout the body.

ENDOMETRIAL CANCER

Cancer of the endometrium, or lining of the uterus, is the most common genital malignancy. It has multiple risk factors, among them obesity, insulin resistance, and diabetes.[33] An early sign of cancerous change is endometrial hyperplasia. Standard therapy for endometrial hyperplasia is treatment with progestogens (progesterone-like hormones), which can restore the endometrium to its normal state. In 2003, researchers at the Mayo Clinic reported a single case study of a woman whose endometrial hyperplasia had failed to respond to progestogen treatment, and who was then given metformin (she was not diabetic).[34] One month after initiation of treatment, the patient's endometrium had returned to its normal state.

In 2010 scientists learned that metformin is a potent inhibitor of endometrial cancer cell proliferation, acting to arrest the cancer cells' reproductive cycle, inducing cell death through apoptosis, and decreasing gene expression of an enzyme complex called human telomerase reverse transcriptase (hTERT) that contributes to unregulated cell replication.[35] Many of these effects were triggered by metformin's activation of the AMP-protein kinase (AMPK) complex, and are identical to those induced by calorie restriction.[35]

Metformin mimics the benefits of a hormone called adiponectin in activating AMPK-dependent growth inhibition in prostate and colon cancer cells.

Based on these observations, other gynecological researchers have begun to use metformin as part of a "conservative" approach (using fewer, less-invasive procedures) to their management of endometrial hyperplasia and endometrial cancer.[36]

PROSTATE CANCER

Prostate cancer is the most-commonly diagnosed cancer in men. Insulin resistance, which triggers rising levels of insulin and insulin-like growth factors (IGFs) substantially increases disease risk.[37,38] For that reason, reducing plasma insulin and IGF levels are significant goals in prostate cancer prevention and treatment, and metformin is increasingly being recommended in those roles.[37]

Metformin mimics the benefits of a hormone called *adiponectin* in activating AMPK-dependent growth inhibition in prostate and colon cancer cells.[38] This helps solidify our understanding of the relationship between obesity, in which adiponectin levels are low, and cancer development.

Metformin also acts by blocking the prostate cancer cells' reproductive cycle by decreasing levels of a cancer growth-promoting protein (cyclin D1), and at the same time increasing production of a protein (p27) that inhibits the cell division cycle.[39] As an aside, it is p27 that is also enhanced (upregulated) by healthy levels of vitamin D, the omega-3 fatty acid DHA, and silibinin—one of the active agents in milk thistle.[40-42] These results testify to metformin's ability to attack cancers from multiple directions at once.

Still another angle from which metformin suppresses prostate cancer is to literally starve the malignant cells of energy, capitalizing on metabolic vulnerabilities unique to cancer cells and absent in healthy cells. Stunning results appeared in early 2010 showing that metformin, in combination with the metabolic agent 2-deoxyglucose, dramatically depletes prostate cancer cells' stores of energy-rich ATP molecules.[43] In fact, the treatment led to a 96% reduction in malignant cells' viability, with only moderate effects on healthy prostate cells. The treatment also triggered a switch from survival processes to cell death in the malignant cells.

These laboratory findings took on profound meaning in a large human study of men with prostate cancer and their use of metformin.[44] Among 1,001 men with prostate cancer and 942 cancer-free controls, metformin use was significantly more common in the control patients, resulting in a risk reduction of **44%.** This finding is especially powerful considering that men taking metformin in this retrospective study were much more likely to have been diabetic, and so their risk for cancer could be expected to have been higher!

PANCREATIC CANCER

Pancreatic cancer is one of the most lethal human diseases, with a nearly-100% fatality rate, and experts are desperate for new biochemical targets that will help control this disease.[45] One such novel target that has been proposed is IGF-GPCR, an interaction between IGF receptors and a powerful group of signaling proteins called G protein-coupled receptors (GPCR). Metformin administration disrupted the IGF-GPCR interaction and thereby significantly decreased the growth of pancreatic cancer cells grafted into susceptible mice.[46]

Metformin also triggers pancreatic cancer cell death by apoptosis by activating caspase, a "death signaling" or "executioner" molecule.[47]

These laboratory findings help explain the remarkable protective effects of metformin in preventing pancreatic cancer in living humans. A large hospital-based case-control study of 973 patients with pancreatic cancer and 863 healthy controls demonstrated a dramatic risk reduction of **62%** in diabetic patients who had taken metformin compared with those who had not.[2] The difference wasn't related solely to reduction in blood sugar, since diabetic patients who had taken insulin or insulin-promoting drugs enjoyed no similar protection. This study, of course, could also be interpreted to show how insulin-promoting drugs and insulin itself increases cancer risk. Life Extension has long warned about the carcinogenic risks associated with elevated insulin levels. Fortunately, another benefit of metformin is reducing insulin and glucose levels via several mechanisms.

FIGHTING OBESITY AND HIGH BLOOD SUGAR

Metformin, originally developed as a simple glucose-lowering drug for type 2 diabetics, is emerging as one of the few true "wonder drugs" of the century. Metformin improves glycemic control, helps prevent and treat obesity, and reduces insulin resistance. And those very characteristics are intimately related to metformin's astonishing anti-cancer properties. Here's an overview of metformin's myriad, multi-targeted effects on obesity and its consequences.

Metformin is first-choice treatment for type 2 diabetes, with especially powerful effects on obese patients with high insulin levels.[53] But metformin is emphatically not just for diabetics. Metformin results in weight loss and improves insulin resistance, even in non-diabetic individuals.[54,55]

We know that poor glycemic control leads to chronic diseases of aging. Reducing blood glucose levels thus has multiple benefits related to general health.

By enhancing insulin sensitivity, metformin protects obese patients from endothelial dysfunction and the cardiovascular disorders that result.[56] Metformin also decreases secretion of a variety of damaging cytokines that, unopposed, light inflammatory fires throughout the body.[57]

And although metformin was long thought to exert its primary effects in the liver and other non-neurological tissues, the drug also has an appetite-suppressing effect on the central nervous system.[58] This all adds up to powerful potential in combating excess body weight.

Two challenging populations provide the best arena for demonstrating metformin's anti-obesity effects. Women with polycystic ovarian syndrome (PCOS) have abnormal sex hormone profiles that can lead to significant obesity despite aggressive dieting. And patients on the newer, second-generation antipsychotic drugs virtually all gain weight, and many develop the metabolic syndrome even at very young ages. Metformin has shown dramatic effects in reducing body weight, BMI, insulin resistance, and other manifestations of disordered metabolism in both of these populations.[57-60]

There's hardly a body system that doesn't benefit in some way from metformin's profound impact. The case of cancer provides a perfect example. We now understand that obesity and its fallout on insulin levels and inflammation are important risk factors for many cancers.[61]

By promoting weight loss, metformin provides documented risk reduction and has crucial direct actions on some of the fundamental molecular pathways that lead to cancer. Those effects are themselves related to metformin's calorie restriction-mimicking effects.[62] Thus, we can see that metformin reduces the risk of obesity and fights cancer by closely interrelated mechanisms, promoting actual weight loss while also triggering the beneficial effects of calorie restriction at the cell and molecular levels.

In a recent example, a team of researchers at Stanford found that metformin significantly **decreases body mass index** in obese, *non*-diabetic adolescents. This marks a promising new advance in the battle against childhood overweight and obesity, which now afflicts almost one third of all children in the United States.[63]

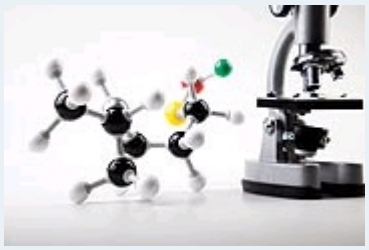
COLON CANCER

Colorectal cancers are major public health problems, being the second most common cancers in developed countries.[48] As with other malignancies, colorectal cancer risk is increased in diabetics, and there is a growing body of evidence that advanced glycation end products (AGEs) and insulin-receptor interactions are involved in initiation of these common tumors.[48,49] Naturally, these findings have piqued scientists' interest in using metformin, which decreases glucose and insulin levels, to prevent colorectal cancer.

Colorectal cancers are among those malignancies most closely associated with obesity.[38] Obese individuals are deficient in the *protective* hormone adiponectin, which activates tumor-suppressing AMPK.[38] Metformin, by independently activating AMPK, may short-circuit this deficiency and help to reduce its impact on colorectal cancer risk.[38]

Metformin has at least one additional pathway by which it prevents colorectal cancer. It is related to the close connection between colon cancer and too many calories. Canadian scientists placed mice on either a normal or a high-calorie diet, and then injected them with viable colon cancer cells.[50] Seventeen days later they examined the tumors that the animals had developed. Tumors from mice on the high-calorie diet were twice the volume of those from normally-fed mice, and their size correlated with elevated insulin levels. Metformin treatment blocked the effect of a high-calorie diet, reducing insulin levels and slowing the growth of tumors. Tumors from metformin-treated mice also showed increased rates of cell death by apoptosis compared with those from untreated animals.

HOW METFORMIN PROTECTS AGAINST CANCER



Like calorie restriction, metformin activates an important molecule called AMPK (adenosine monophosphate-activated protein kinase) which senses cellular energy status.[64] AMPK is activated by a variety of cellular stresses including decreased energy availability—a known result of calorie restriction. It also modulates multiple metabolic pathways.[65]

In the liver, AMPK reduces production of new glucose molecules, indirectly reducing levels of insulin and insulin-like growth factors (IGFs).[66] That's how metformin works to correct type 2 diabetes. But throughout the body, AMPK activation stimulates fatty acid oxidation, enhances insulin sensitivity, alleviates hyperglycemia and hyperlipidemia, and inhibits prolinflammatory changes.[67] Those effects alone could be expected to have substantial anti-cancer benefits, in light of what we know about the role of glucose, insulin, IGFs, and inflammation in cancer development.[68]

But there's more. Cancer cells have metabolic characteristics different from normal cells, making them vulnerable to metabolic manipulation (as opposed to chemotherapy's imprecise, wholesale poisoning of all body tissues).[69] So in cancer cells, AMPK activation triggers a unique cascade of molecular events that collaborate to suppress cancers.[67,70] AMPK activation suppresses cancer cell proliferation; it does this by blocking the gene expression of specific cancer-promoting proteins.[30,66] AMPK activation also breaks a critical link between obesity and postmenopausal breast cancer by blocking estrogen production within the breast tissue.[21]

Laboratory studies have now demonstrated that metformin's AMPK activation, and reduction of IGF, can suppress development and growth of cancer cells from breast, ovary, pancreas, and many other tissues.[45,62,71,72] One of the most heartening findings has been the effectiveness of metformin against even some of the most aggressive forms of breast cancers, which disproportionately affect younger women.[23,66]

REPORT

The Drug Virtually Everyone Should Ask their Doctor About

By Julius Goepp, MD

LUNG CANCER

More men and women die from lung cancer than from any other malignancy. In 2006, lung cancer caused more deaths than breast cancer, colon cancer, and prostate cancer combined.[51] Clearly, new solutions to fighting lung cancer are greatly needed. Emerging research suggests that metformin may offer hope in combating this deadly disease.

A NEW PATHWAY FOR CANCER REDUCTION

There is late-breaking news that there is now an additional mechanism by which metformin can reduce the risk of cancer and metabolic disorders.

A molecular complex called mammalian target of rapamycin (mTOR) functions as a "metabolic integrator," receiving inputs about energy and stress levels and translating them into cellular actions.[73-75] And when mTOR signaling goes awry, it triggers numerous events, including those leading to a variety of cancers.[76] Aberrant mTOR activation, in fact, has now been added to the list of biochemical abnormalities that contribute to many of the chronic diseases of aging.[77,78]

Calorie restriction inhibits the action of mTOR, thereby reducing the risk of many diseases of aging.[79,80] Scientists have known for a decade that metformin inhibits mTOR in a fashion similar to calorie restriction. But until recently they'd thought that the mTOR inhibition was simply another result of metformin's AMPK activation.[46,81,82]

George Thomas, PhD, scientific director of the Metabolic Diseases Institute at the University of Cincinnati[83] and his colleagues have discovered that metformin efficiently inhibits mTOR—completely independent of its effect on AMPK.[76] That supports and extends the few previous studies that had shown an AMPK-independent action for metformin.[84-87] Together these findings have tremendous implications; Thomas himself recently said this, ***"Metformin is already prescribed to 100 million people worldwide, and our study raises the question, 'Could this drug be used even more widely?'***[83]

The fact is that mTOR inhibitor drugs have been in use for at least 5 years, primarily in managing transplant rejection, and recently in certain forms of cancer.[88-90] But these drugs, based on a failed antifungal drug called rapamycin (also called sirolimus), have tremendous toxicity. Fortunately in mid-2010, a lab study demonstrated greater anticancer effects with metformin than with rapamycin.[91]

The discovery of metformin's direct mTOR-inhibitory effects, then, means this dramatically new mechanism of action is available to thousands of people who would have had no options other than facing the toxicity of the traditional mTOR inhibitors.

In a recent study, scientists examined the effects of metformin on an experimental form of lung cancer that is especially aggressive in obese subjects with high blood sugar. Animal subjects received either a control diet or a high-energy diet that typically leads to weight gain and insulin resistance, and selected subjects received metformin in their drinking water. After three weeks, the subjects were injected with lung cancer cells. Seventeen days later, animals on the high-energy diet had tumors that were twice the volume of animals on the control diet. Metformin significantly attenuated tumor growth in subjects consuming a high-energy diet. Metformin led to increased phosphorylation of AMPK and attenuated the increased insulin receptor activation association with a high-energy diet—both of which would be expected to decrease cancer proliferation.[3]

Additional research suggests that metformin may enhance the effects of radiation therapy in eradicating lung and other cancers.[52]

While further studies are needed, these findings suggest that metformin may offer promise in the fight against lung cancer.

METFORMIN MAY HELP TREAT HEPATITIS C INFECTION

New research suggests that anti-diabetic drugs such as metformin and AICAR, currently used to fight obesity, may benefit patients with hepatitis C by preventing replication of the virus in the body.92 Hepatitis affects about 3% of the world's

population, many of whom will develop cirrhosis or liver cancer. Currently there is no vaccine or cure.

Metformin and AICAR work by stimulating the cellular energy-regulating enzyme AMPK, which the hepatitis C virus represses in order to replicate. When hepatitis C-infected cells were treated with metformin, virus replication was halted, allowing cells to clear the infection.

Based on this finding, a clinical trial will begin shortly at the University of Nottingham to explore metformin's applications in the management of hepatitis C.

SUMMARY

The list of cancers against which metformin is protective is growing rapidly, now including cancers of the prostate, pancreas, liver, lung, and other tissues.[3,16,95,96] Since metformin acts by multiple pathways, most of which are fundamental to every kind of cancer, there's no reason to think that these results won't in fact be generalizable to every human malignancy.

The key fact about metformin is its ability, shared with other nutraceuticals but rare among other prescription drugs, to potently mimic the effects of calorie restriction. Metformin's calorie restriction-like effects trigger profound cellular changes in every mammalian tissue, activating tumor suppressing mechanisms while suppressing tumor activating mechanisms. By lowering chronic blood sugar levels and limiting lifetime exposure to insulin and insulin-like growth factors, metformin can directly reduce cancer risks related to these factors.

The wealth of evidence of metformin's anti-cancer activity is now expanding to include not only those with diabetes or pre-diabetic conditions, but also people who are apparently otherwise healthy. This means that anyone who is serious about a comprehensive approach to cancer prevention should give serious consideration to using metformin just as faithfully as they use other calorie restriction-mimetic supplements.

Those seeking to gain the longevity benefits associated with reduced glucose and insulin levels can benefit tremendously from metformin.

WHO CANNOT USE METFORMIN

Metformin has been associated with an increase risk of lactic acidosis, a rare but potentially fatal buildup of lactic acid in the blood. Since congestive heart failure, kidney impairment, and liver problems increase the risk of lactic acidosis, individuals with these conditions are advised against using metformin. People with metabolic ketoacidosis and people taking both gemfibrozil and itraconazole should not take metformin.[93] Individuals with type 1 diabetes should also not take the drug. People who have recently suffered a heart attack or stroke and those who have recently undergone surgery or are severely dehydrated are more vulnerable to lactic acidosis.[94] Consult with your doctor if any of these conditions applies to you or if you are pregnant, planning to become pregnant, or breastfeeding.

Lactic acidosis is a medical emergency. Symptoms include muscle pain, difficulty breathing, sleepiness, feeling extremely weak or tired, and abdominal pain with nausea, vomiting, or diarrhea.[93]

There have been some reports that metformin can decrease TSH levels in people with an underactive thyroid or Hashimoto's thyroiditis. These reports suggest that metformin may suppress TSH levels, perhaps without effecting thyroid hormone levels. However, more studies involving larger groups of people are needed before any conclusions can be made about metformin, TSH level, and thyroid hormone levels.[97,98]

As you read in last month's issue, optimal fasting glucose should be around **80** mg/dL. Metformin can help aging humans achieve these lower and healthier glucose levels. Typical doses are **250** mg to **850** mg taken before two or three meals each day. Refer to the box on the following page for information about who should not take metformin.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

METFORMIN MAY PROTECT SMOKERS AGAINST LUNG AND COLORECTAL CANCER

Two recent articles in the medical journal *Cancer Prevention Research* reveal that smokers may have a much lower risk of suffering lung cancer and colorectal cancer if they take the drug metformin.

Metformin is a popular drug used to combat diabetes type 2, however, two studies show it holds promise as an anticancer drug as well. A study conducted by the scientists at the National Cancer Institute, led by Dr. Philip Dennis, revealed a significantly

lower lung cancer tumor rate in mice that were given metformin and exposed to a prevalent tobacco carcinogen.[97] The mice injected with metformin had 72% fewer tumors.

A second study conducted by scientists in Japan revealed that non-diabetic individuals who took metformin had a considerably reduced rate of rectal aberrant crypt foci, a surrogate marker of colorectal cancer.[98]

References

1. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care. 2010 Jun;33(6):1304-8.

2. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology. 2009 Aug;137(2):482-8.

3. Algire C, Zakikhani M, Blouin MJ, Shuai JH, Pollak M. Metformin attenuates the stimulatory effect of a high-energy diet on in vivo LLC1 carcinoma growth. Endocr Relat Cancer. 2008 Sep;15(3):833-9.

4. Witters LA. The blooming of the French lilac. J Clin Invest. 2001 Oct;108(8):1105-7.

5. Vuksan V, Sievenpiper JL. Herbal remedies in the management of diabetes: lessons learned from the study of ginseng. Nutr Metab Cardiovasc Dis. 2005 Jun;15(3):149-60.

6. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. Drugs. 2003;63(18):1879-94.

7. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care. 2002 Dec;25(12):2244-8.

8. Gosmanova EO, Canada RB, Mangold TA, Rawls WN, Wall BM. Effect of metformin-containing antidiabetic regimens on all-cause mortality in veterans with type 2 diabetes mellitus. Am J Med Sci. 2008 Sep;336(3):241-7.

9. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care. 2005 Oct;28(10):2345-51.

10. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia. 2006 May;49(5):930-6.

11. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. 2006 Feb;29(2):254-8.

12. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009 Sep;52(9):1766-77.

13. Duncan BB, Schmidt MI. Metformin, cancer, alphabet soup, and the role of epidemiology in etiologic research. Diabetes Care. 2009 Sep;32(9):1748-50.

14. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care. 2010 Feb;33(2):322-6.

15. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005 Jun 4;330(7503):1304-5.

16. Czyzyk A, Szczepanik Z. Diabetes mellitus and cancer. Eur J Intern Med. 2000 Oct;11(5):245-52.

17. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009 Dec;16(4):1103-23.

18. Martin-Castillo B, Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA. Metformin and cancer: Doses, mechanisms and the dandelion and hormetic phenomena. Cell Cycle. 2010 Mar 21;9(6).

19. Anisimov VN, Egormin PA, Piskunova TS, et al. Metformin extends life span of HER-2/neu transgenic mice and in

combination with melatonin inhibits growth of transplantable tumors in vivo. Cell Cycle. 2010 Jan 1;9(1):188-97.

20. Phoenix KN, Vumbaca F, Fox MM, Evans R, Claffey KP. Dietary energy availability affects primary and metastatic breast cancer and metformin efficacy. Breast Cancer Res Treat. 2009 Nov 22.

21. Brown KA, Hunger NI, Docanto M, Simpson ER. Metformin inhibits aromatase expression in human breast adipose stromal cells via stimulation of AMP-activated protein kinase. Breast Cancer Res Treat. 2010 Mar 19.

22. Yurekli BS, Karaca B, Cetinkalp S, Uslu R. Is it the time for metformin to take place in adjuvant treatment of Her-2 positive breast cancer? Teaching new tricks to old dogs. Med Hypotheses. 2009 Oct;73(4):606-7.

23. Gonzalez-Angulo AM, Meric-Bernstam F. Metformin: a therapeutic opportunity in breast cancer. Clin Cancer Res. 2010 Mar 15;16(6):1695-700.

24. Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA. The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. Cell Cycle. 2009 Jan 1;8(1):88-96.

25. Olayioye MA. Update on HER-2 as a target for cancer therapy: intracellular signaling pathways of ErbB2/HER-2 and family members. Breast Cancer Res. 2001;3(6):385-9.

26. Zhuang Y, Miskimins WK. Cell cycle arrest in Metformin treated breast cancer cells involves activation of AMPK, downregulation of cyclin D1, and requires p27Kip1 or p21Cip1. J Mol Signal. 2008;3:18.

27. Hirsch HA, Iliopoulos D, Tsichlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res. 2009 Oct 1;69(19):7507-11.

28. Alimova IN, Liu B, Fan Z, et al. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. Cell Cycle. 2009 Mar 15;8(6):909-15.

29. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol. 2009 Jul 10;27(20):3297-302.

30. Liu B, Fan Z, Edgerton SM, et al. Metformin induces unique biological and molecular responses in triple negative breast cancer cells. Cell Cycle. 2009 Jul 1;8(13):2031-40.

31. Martin-Castillo B, Dorca J, Vazquez-Martin A, et al. Incorporating the antidiabetic drug metformin in HER2-positive breast cancer treated with neo-adjuvant chemotherapy and trastuzumab: an ongoing clinical-translational research experience at the Catalan Institute of Oncology. Ann Oncol. 2010 Jan;21(1):187-9.

32. Garcia A, Tisman G. Metformin, B(12), and enhanced breast cancer response to chemotherapy. J Clin Oncol. 2010 Jan 10;28(2):e19; author reply e20.

33. Kacalska O, Krzyczkowska-Sendrakowska M, Milewicz T, et al. Molecular action of insulin-sensitizing agents. Endokrynol Pol. 2005 May-Jun;56(3):308-13.

34. Session DR, Kalli KR, Tummon IS, Damario MA, Dumesic DA. Treatment of atypical endometrial hyperplasia with an insulin-sensitizing agent. Gynecol Endocrinol. 2003 Oct;17(5):405-7.

35. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation--implications for a novel treatment strategy. Gynecol Oncol. 2010 Jan;116(1):92-8.

36. Stanosz S. An attempt at conservative treatment in selected cases of type I endometrial carcinoma (stage I a/G1) in young women. Eur J Gynaecol Oncol. 2009;30(4):365-9.

37. Guastamacchia E, Resta F, Triggiani V, et al. Evidence for a putative relationship between type 2 diabetes and neoplasia with particular reference to breast cancer: role of hormones, growth factors and specific receptors. Curr Drug Targets Immune Endocr Metabol Disord. 2004 Mar;4(1):59-66.

38. Zakikhani M, Dowling RJ, Sonenberg N, Pollak MN. The effects of adiponectin and metformin on prostate and colon neoplasia

involve activation of AMP-activated protein kinase. Cancer Prev Res (Phila Pa). 2008 Oct;1(5):369-75.

39. Ben Sahra I, Laurent K, Loubat A, et al. The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. Oncogene. 2008 Jun 5;27(25):3576-86.

40. Raina K, Blouin MJ, Singh RP, et al. Dietary feeding of silibinin inhibits prostate tumor growth and progression in transgenic adenocarcinoma of the mouse prostate model. Cancer Res. 2007 Nov 15;67(22):11083-91.

41. Khan NA, Nishimura K, Aires V, et al. Docosahexaenoic acid inhibits cancer cell growth via p27Kip1, CDK2, ERK1/ERK2, and retinoblastoma phosphorylation. J Lipid Res. 2006 Oct;47(10):2306-13.

42. Johnson CS, Muindi JR, Hershberger PA, Trump DL. The antitumor efficacy of calcitriol: preclinical studies. Anticancer Res. 2006 Jul-Aug;26(4A):2543-9.

43. Ben Sahra I, Laurent K, Giuliano S, et al. Targeting cancer cell metabolism: the combination of metformin and 2-deoxyglucose induces p53-dependent apoptosis in prostate cancer cells. Cancer Res. 2010 Mar 15;70(6):2465-75.

44. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. Cancer Causes Control. 2009 Nov;20(9):1617-22.

45. Rozengurt E, Sinnett-Smith J, Kisfalvi K. Crosstalk between insulin/insulin-like growth factor-1 receptors and G protein-coupled receptor signaling systems: a novel target for the antidiabetic drug metformin in pancreatic cancer. Clin Cancer Res. 2010 Apr 13.

46. Kisfalvi K, Eibl G, Sinnett-Smith J, Rozengurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. Cancer Res. 2009 Aug 15;69(16):6539-45.

47. Wang LW, Li ZS, Zou DW, Jin ZD, Gao J, Xu GM. Metformin induces apoptosis of pancreatic cancer cells. World J Gastroenterol. 2008 Dec 21;14(47):7192-8.

48. Yamagishi S, Nakamura K, Inoue H, Kikuchi S, Takeuchi M. Possible participation of advanced glycation end products in the pathogenesis of colorectal cancer in diabetic patients. Med Hypotheses. 2005;64(6):1208-10.

49. Mountjoy KG, Finlay GJ, Holdaway IM. Effects of metformin and glibenclamide on insulin receptors in fibroblasts and tumor cells in vitro. J Endocrinol Invest. 1987 Dec;10(6):553-7.

50. Algire C, Amrein L, Zakikhani M, Panasci L, Pollak M. Metformin blocks the stimulative effect of a high-energy diet on colon carcinoma growth in vivo and is associated with reduced expression of fatty acid synthase. Endocr Relat Cancer. 2010 Jun;17 (2):351-60.

51. Available at: http://www.cdc.gov/cancer/lung/statistics/. Accessed August 3, 2010.

52. Sanli T, Rashid A, Liu C,et al. Ionizing radiation activates AMP-activated kinase (AMPK): a target for radiosensitization of human cancer cells. Int J Radiat Oncol Biol Phys. 2010 Jul 7.

53. Mehnert H. Metformin, the rebirth of a biguanide: mechanism of action and place in the prevention and treatment of insulin resistance. Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S259-64.

54. Desilets AR, Dhakal-Karki S, Dunican KC. Role of metformin for weight management in patients without type 2 diabetes. Ann Pharmacother. 2008 Jun;42(6):817-26.

55. Golay A. Metformin and body weight. Int J Obes (Lond). 2008 Jan;32(1):61-72.

56. Brame L, Verma S, Anderson T, Lteif A, Mather K. Insulin resistance as a therapeutic target for improved endothelial function: metformin. Curr Drug Targets Cardiovasc Haematol Disord. 2004 Mar;4(1):53-63.

57. Tan BK, Heutling D, Chen J, et al. Metformin decreases the adipokine vaspin in overweight women with polycystic ovary syndrome concomitant with improvement in insulin sensitivity and a decrease in insulin resistance. Diabetes. 2008 Jun;57 (6):1501-7.

58. Ehret M, Goethe J, Lanosa M, Coleman CI. The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: a meta-analysis. J Clin Psychiatry. 2010 Apr 6.

59. Ellinger LK, Ipema HJ, Stachnik JM. Efficacy of metformin and topiramate in prevention and treatment of second-generation antipsychotic-induced weight gain. Ann Pharmacother. 2010 Apr;44(4):668-79.

60. Aghahosseini M, Aleyaseen A, Safdarian L, Moddaress-Hashemi S, Mofid B, Kashani L. Metformin 2,500 mg/day in the treatment of obese women with polycystic ovary syndrome and its effect on weight, hormones, and lipid profile. Arch Gynecol Obstet. 2010 Jul 2.

61. Wysocki PJ, Wierusz-Wysocka B. Obesity, hyperinsulinemia and breast cancer: novel targets and a novel role for metformin. Expert Rev Mol Diagn. 2010 May;10(4):509-19.

62. Anisimov VN, Berstein LM, Egormin PA, et al. Effect of metformin on life span and on the development of spontaneous mammary tumors in HER-2/neu transgenic mice. Exp Gerontol. 2005 Aug-Sep;40(8-9):685-93.

63. Wilson DM, Abrams SH, Aye T, et al. Metformin extended release treatment of adolescent obesity: A 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. Arch Pediatr Adolesc Med. 2010 Feb;164(2):116-23.

64. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer. 2008 Dec;8(12):915-28.

65. Sanz P. AMP-activated protein kinase: structure and regulation. Curr Protein Pept Sci. 2008 Oct;9(5):478-92.

66. Jiralerspong S, Gonzalez-Angulo AM, Hung MC. Expanding the arsenal: metformin for the treatment of triple-negative breast cancer? Cell Cycle. 2009 Sep 1;8(17):2681.

67. Luo Z, Zang M, Guo W. AMPK as a metabolic tumor suppressor: control of metabolism and cell growth. Future Oncol. 2010 Mar;6(3):457-70.

68. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009 Sep;32(9):1620-5.

69. Wang W, Guan KL. AMP-activated protein kinase and cancer. Acta Physiol (Oxf). 2009 May;196(1):55-63.

70. Vazquez-Martin A, Oliveras-Ferraros C, Lopez-Bonet E, Menendez JA. AMPK: Evidence for an energy-sensing cytokinetic tumor suppressor. Cell Cycle. 2009 Nov 15;8(22):3679-83.

71. Oliveras-Ferraros C, Vazquez-Martin A, Menendez JA. Genome-wide inhibitory impact of the AMPK activator metformin on [kinesins, tubulins, histones, auroras and polo-like kinases] M-phase cell cycle genes in human breast cancer cells. Cell Cycle. 2009 May 15;8(10):1633-6.

72. Rattan R, Giri S, Hartmann L, Shridhar V. Metformin attenuates ovarian cancer cell growth in an AMP- kinase dispensable manner. J Cell Mol Med. 2009 Oct 29.

73. Kim DH, Sarbassov DD, Ali SM, et al. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell. 2002 Jul 26;110(2):163-75.

74. Tokunaga C, Yoshino K, Yonezawa K. mTOR integrates amino acid- and energy-sensing pathways. Biochem Biophys Res Commun. 2004 Jan 9;313(2):443-6.

75. Choo AY, Kim SG, Vander Heiden MG, et al. Glucose addiction of TSC null cells is caused by failed mTORC1-dependent balancing of metabolic demand with supply. Mol Cell. 2010 May 28;38(4):487-99.

76. Kalender A, Selvaraj A, Kim SY, et al. Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. Cell Metab. 2010 May 5;11(5):390-401.

77. Sakuma K, Yamaguchi A. Molecular mechanisms in aging and current strategies to counteract sarcopenia. Curr Aging Sci. 2010 Jul 1;3(2):90-101.

78. Sudarsanam S, Johnson DE. Functional consequences of mTOR inhibition. Curr Opin Drug Discov Devel. 2010 Jan;13(1):31-

40.

79. Blagosklonny MV. Calorie restriction: decelerating mTOR-driven aging from cells to organisms (including humans). Cell Cycle. 2010 Feb;9(4):683-8.

80. Ghosh HS, McBurney M, Robbins PD. SIRT1 negatively regulates the mammalian target of rapamycin. PLoS One. 2010;5 (2):e9199.

81. Shaw RJ. LKB1 and AMP-activated protein kinase control of mTOR signalling and growth. Acta Physiol (Oxf). 2009 May;196 (1):65-80.

82. Jalving M, Gietema JA, Lefrandt JD, et al. Metformin: Taking away the candy for cancer? Eur J Cancer. 2010 Jul 23.

83. Available at:http://www.sciencedaily.com/releases/2010/05/100504124344.htm#.Accessed July 28, 2010.

84. Saeedi R, Parsons HL, Wambolt RB, et al. Metabolic actions of metformin in the heart can occur by AMPK-independent mechanisms. Am J Physiol Heart Circ Physiol. 2008 Jun;294(6):H2497-506.

85. Ota S, Horigome K, Ishii T, et al. Metformin suppresses glucose-6-phosphatase expression by a complex I inhibition and AMPK activation-independent mechanism. Biochem Biophys Res Commun. 2009 Oct 16;388(2):311-6.

86. Miller RA, Birnbaum MJ. An energetic tale of AMPK-independent effects of metformin. J Clin Invest. 2010 Jul 1;120(7):2267-70.

87. Foretz M, Hebrard S, Leclerc J, et al. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J Clin Invest. 2010 Jul 1;120(7):2355-69.

88. Vazquez-Martin A, Oliveras-Ferraros C, del Barco S, Martin-Castillo B, Menendez JA. mTOR inhibitors and the anti-diabetic biguanide metformin: new insights into the molecular management of breast cancer resistance to the HER2 tyrosine kinase inhibitor lapatinib (Tykerb). Clin Transl Oncol. 2009 Jul;11(7):455-9.

89. Monaco AP. The role of mTOR inhibitors in the management of posttransplant malignancy. Transplantation. 2009 Jan 27;87 (2):157-63.

90. Albert S, Serova M, Dreyer C, Sablin MP, Faivre S, Raymond E. New inhibitors of the mammalian target of rapamycin signaling pathway for cancer. Expert Opin Investig Drugs. 2010 Aug;19(8):919-30.

91. Zakikhani M, Blouin MJ, Piura E, Pollak MN. Metformin and rapamycin have distinct effects on the AKT pathway and proliferation in breast cancer cells. Breast Cancer Res Treat. 2010 Aug;123(1):271-9.

92. Available at: http://www.medicalnewstoday.com/articles/191197.php. Accessed July 29, 2010.

93. Available at: http://www.pdrhealth.com/drugs/rx/rx-mono.aspx?
contentFileName=pra1968.html&contentName=PrandiMet&contentId=595. Accessed August 2, 2010.

94. Available at: http://www.rxlist.com/glucophage-drug.htm. Accessed August 3, 2010

95. Donadon V, Balbi M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: potential role of insulin. World J Gastroenterol. 2008 Oct 7;14(37):5695-700.

96. Donadon V, Balbi M, Zanette G. Hyperinsulinemia and risk for hepatocellular carcinoma in patients with chronic liver diseases and Type 2 diabetes mellitus. Expert Rev Gastroenterol Hepatol. 2009 Oct;3(5):465-7.

97. Available at: http://diabetes.emedtv.com/metformin/metformin-and-tsh-levels.html. Accessed August 31, 2010.

98. Available at: http://care.diabetesjournals.org/content/32/9/1589.full. Accessed August 31, 2010.

99. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD, Dennis PA. Metformin prevents tobacco carcinogen-induced lung tumorigenesis. Cancer Prev Res. 2010 Sept; 3:1066.

100. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. Cancer Prev Res. 2010 Sept; 3:1077.

***These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure or prevent any disease.**