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Review

Metformin as Cancer Preventative and Therapeutic Agent

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Metformin (dimethylbiguanide) is an anti-diabetic drug that serves to keep blood sugar levels under control. Metformin, which is on the World Health Organization's list of essential medicines, belongs to the biguanide class and has similar effects to sulfonylureas, thiazolidinediones, and insulin in lowering blood sugar levels.[1-4] In contrast to other antihyperglycemic drug classes, metformin is the first-line drug for patients with type 2 diabetes mellitus (T2DM), whether as monotherapy or in combination.[5] In addition, the use of metformin is not limited to T2DM alone; it is also used in various diseases such as polycystic ovary syndrome, and non-alcoholic fatty liver disease.[6] While it has tolerable side effects including nausea, diarrhea, and gas issues in first-time patients, these side effects fade with time, which has encouraged people to use it.[7] Eventually, the discovery of anticancer effects has led metformin to a brand new area of use such as 'oncology'.[8] Targeting the energy metabolism of cancer cells, which is one of the important issues in oncology in recent years, has led to intensive research and studies in this area with metformin.[9,10] The anticancer properties of metformin and its present role in cancer treatment were discussed in this review.

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ABSTRACT

Metformin is a biguanide drug that is commonly used to treat type 2 diabetes mellitus (T2DM). According to a meta-analysis, T2DM patients have a much higher risk of developing cancer than healthy people. Long-term trials in T2DM patients treated with metformin have revealed a reduction in cancer incidence. Moreover, metformin use in type 2 diabetic cancer patients was also associated with decreases in cancer-related recurrence, metastasis, and also mortality. Metformin has been shown in vivo and in vitro experiments to inhibit tumor proliferation, induce apoptosis, and stimulate autophagy in tumor cells. All these studies have been directed to the use of metformin as an anticancer agent in cancer treatment, with or without T2DM, since it confirms that metformin has an anti-tumor effect. In this review, the anticancer effects of metformin and its current place in cancer treatment were discussed.

Keywords: Anti-tumor effects, cancer treatment, diabetes mellitus, metformin, type 2 diabetes mellitus

METFORMIN AS AN ANTI-CANCER AGENT

The antihyperglycemic effect of metformin on cells is very complex and still not fully explained. Primarily, it shows its effect by suppressing glucose production in the liver. It reduces insulin resistance in peripheral tissues and increases glucose utilization in skeletal muscle.[11,12] Metformin's anticancer role can be explained by the amount of insulin in the blood. Metformin decreases the plasma insulin/insulin-like growth factor 1 (IGF-1) level by increasing the glucose uptake of skeletal muscle cells. Therefore, the growth of neoplastic or pre-neoplastic cells is inhibited.[13]

In the mechanism at the intracellular level, It mainly provides its effect by activation of AMP-activated protein kinase (AMPK). This activation occurs through liver kinase B1 (LKB1). AMPK is an energy sensor and regulator in cellular power plants that senses the adenosine monophosphate/triphosphate balance. This protein controls the amount of energy in the cell and decides whether fats and carbohydrates are stored

or spent in order to produce energy. In the absence of food, AMPK inhibits energy-consuming mechanisms and activates energy-generating mechanisms. One of the main growth pathways controlled by AMPK is the mammalian target of rapamycin (mTOR). The mTOR controls cell growth and angiogenesis by regulating growth factors. The escape of cancer cells from proliferation and apoptosis is related to mTOR.[14-16]

The effect of AMPK on cancer cells has also been researched, given these energy pathways and their role in cell division. Wheaton et al.[17] found that when metformin was applied to cancer cells in a laboratory environment, programmed cell death happened.[18] It follows that the AMPK protein can induce apoptosis in cancer cells by cutting off their energy.

Retrospective, long-term field trials, and analyses showed significantly lower cancer prevalence in patients with T2DM who had a high risk of developing cancer while taking metformin.[19,20]

Metformin's anti-tumoral activity has also been associated with an increase in cancer patients' life expectancy. As a result of these studies, it has been determined that metformin is an effective agent, especially in colorectal, breast, gynecological, and lung cancer, and significantly prolongs the life span of cancer patients.[8,21]

METFORMIN AND COLORECTAL CANCER

Colorectal cancer (CRC) occurs in the large intestine's colon or rectum. While colon cancer can affect someone at any age, the majority of patients are in their fifties or older. Those with a family history of colon cancer, polyps, or inflammatory bowel disease are at a higher risk. This cancer is caused by polyps of the adenoma type, which are most commonly found in the intestinal condition's treatment, even 40% of patients diagnosed in the early stages of the disease suffer cancer recurrence.[22-24] This has led to the search for effective anti-tumoral options during or after cancer treatment.

In the first report published in 2004, the relationship between CRC and T2DM treatment was considered. In this research, an increased incidence of CRC was found in patients using chronic insulin, while metformin was not seen as an agent that increases the incidence of CRC.[25] In a 2008 study, Zakikhani et al.[26] discovered that metformin, depending on its intracellular concentration, inhibits the proliferation of human colon cancer cell line HT-29 cells. By activating the energy pathway AMPK, it inhibits HT-29 cells.

Another *in vitro* study tested the proliferation of SW-480 cells, which is in the colorectal cancer line, treated with different metformin concentrations. As a result, metformin was observed that SW-480 cells decreased depending on the dose and time. It was observed that metformin mainly inhibits the growth of SW-480 cells by blocking the G0/G1 cell cycle and decreasing cyclin D1 expression.[27]

In recent *in vivo* and *in vitro* studies, it has been observed that metformin supports apoptotic and autophagic cell death by suppressing the activation of nuclear factor E2-associated factor 2 (NRF2) and nuclear factor kappa B (NF-κB) in HT29 cells. It is also thought that metformin influences the methylation status of the tumor suppressor gene Ras-association domain family protein1 isoform A (RASSF1A), which inhibits apoptosis and cell migration.[28, 29]

Ultimately, the anticancer effects of metformin were supported by data from two large-scale, population-based, case-control trials on the etiology of colorectal and breast cancer performed in Northern Israel in 1998. Metformin usage before a cancer diagnosis has been associated with a decreased incidence of colorectal and breast cancer.[30]

METFORMIN AND BREAST CANCER

Breast cancer starts in the cells of the breast. According to statistics from 2021, it is the cancer type with the largest global prevalence and one out of every eight women will develop breast cancer at any time in life. It is the world's second most common cause of cancer mortality in women, and, like other cancers, early detection is critical for treatment.[23,31] Beginning to study breast cancer at the molecular level has enabled the mutations in the relevant genes to find different energy pathways. It has been made possible by linking metformin with breast cancer treatment through these energy pathways.

In both *in vitro* and *in vivo* tumor models, metformin has been shown to suppress the growth of cancer cells, including breast cancer lines. Metformin reduces the prevalence of breast cancer in diabetic patients and cancer-related death, as well as increases the response to neoadjuvant chemotherapy and radiotherapy in breast cancer patients, according to population and retrospective research.[32, 33]

Metformin's anticancer activity on breast tumor cells is also demonstrated by AMPK activation. AMPK prevents lipid and sterol biosynthesis by phosphorylating enzymes including acetyl-CoA carboxylase (ACC), fatty acid synthase

(FAS), and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.[34] Patients with hormone receptor-positive breast cancer are more likely to benefit from this situation. According to a study of 5464 people, metformin usage significantly increased overall survival in hormone-positive breast cancer patients (65%).[35]

Insulin/IGF-1, also known as a cell division stimulator independent of AMPK, is often found in high concentrations in cancer cells, including breast cancer. Metformin has also been shown in experiments to suppress IGF1 and, as a result, to inhibit the development of neoplastic cells.[36,37]

Metformin has been shown to induce cell cycle progression in breast cancer cell lines in hormone receptor-negative patients with an aggressive prognosis, i.e. triple-negative breast cancer (TNBC).[38] It has been determined that metformin specifically reduces the expression of key glucose transporters in TNBC such as glucose transporter 1 (GLUT1).[39]

In population-based and large research, the elucidation of these molecular pathways, as well as the anti-tumor effects of metformin, has been recognized. A population-based study was linked with an increased prevalence of breast cancer in T2DM patients in a major analysis of 44.541 people performed in 2021 by Park et al.[40], indicating that long-term use of metformin in hormone receptor status would decrease the risk of breast cancer progressing with T2DM.

METFORMIN AND GYNECOLOGICAL CANCERS

Gynecological cancers constitute one-fifth of solid cancers seen in women. It is the general name given to cancers in the cervix, ovary, uterus, fallopian tubes, vagina, endometrium, or vulva. Endometrial cancer, ovarian cancer, and cervical cancer are the three most common gynecological cancers in women.[41]

Metformin is a gynecological medication used to treat polycystic ovary syndrome (PCOS). PCOS is a disorder in which a woman's ovaries produce a large number of cysts, causing hormonal imbalance.[42] In addition to PCOS, the development of insulin resistance is also closely related to the development of T2DM and gynecological cancers.[43]

Metformin's action in the treatment of endometrial cancer is primarily based on cellular AMPK activation, followed by inhibition of multiple metabolic pathways such as ACC, mTOR, and Insulin/IGF-1. These lead to decreased protein and fatty acid synthesis in tumor cells, slow cell cycle progression, and ultimately apoptosis and autophagy, both of which have been linked to gynecological cancers.[44]

Forkhead Box O3 (FOXO3) is a transcription factor that regulates many expressions such as deoxyribonucleic acid (DNA) repair, apoptosis, energy metabolism, and regulation of cell cycle progression. p53 is a tumor suppressor that plays important role in apoptosis, cellular aging, and autophagy.[45] The transport of FOXO3 into the nucleus with p53 increased after low-dose metformin treatment of OVCA429 ovarian cancer cells. In accordance with research, the cell cycle was stopped, and the expression of some stem cell biomarkers such as CD44 was reduced.[46] Patients with atypical endometrial hyperplasia, a premalignant lesion, are linked with the transfer of patients to normal endometrial histology due to the use of metformin, as well as a decrease in biomarkers involved in tumor progression, according to a study published by Meireles et al.[47] This observation has led to the idea that metformin could cause cancer cells to be reprogrammed into noncancerous tissues.

Metformin has also been associated with enhanced chemotherapy responses in gynecological cancers. It works in conjunction with chemotherapy to selectively kill cancer stem cells, according to a report performed in the laboratory environment.[48] Metformin has been shown to reduce the risk of endometrial cancer in a population-based analysis. Metformin increases recurrence-free and overall survival in diabetic patients with endometrial cancer, according to studies.[49]

Metformin emphasized that is a possible antitumor agent in preventing gynecological cancers, particularly cervical cancers, in a very broad data scan and meta-analysis of 1.7 million patients by Wen et al.[50]

METFORMIN AND LUNG CANCER

Lung cancer is a tumor that grows as cells in the lungs become cancerous. While there are several histological subtypes of lung cancer, the two most common groups are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and the therapeutic course is determined by this classification. The anti-cancer effects of metformin, which is used as a diabetic agent, as in other cancers are mainly explained by its activation of AMPK, the inhibition of mTOR hyperactivity, and its effect by reducing the

amount of Insulin/IGF-1 that induces mitogenesis.[26]

Metformin's anti-cancer properties have also been confirmed *in vitro* studies of lung cancer cells. Metformin treatment of A549, RERF-LC-A1, IA-5, and WA-hT cells, which are in the lung cancer tissue line, resulted in cell apoptosis and decreased colony development. G0/G1 induced cell arrest in certain tumor cells.[51,52]

Metformin's anti-tumor properties in the lungs have been shown *in vitro*. According to a rat study, metformin prevents the growth of tumors with positive for the KRAS mutation lung cancer cells and it does this by reducing the mTOR signal.[53] In another study, using metformin and kinase inhibitors for a while in rats injected with A549 cells was linked to better treatment response and a reduction in tumor size.[54]

Clinical trials have promoted that metformin has anti-tumor properties. Yao et al.[55] checked the connection between diabetes and lung cancer and found that patients taking metformin had a lower risk of lung cancer. In other clinical trials of metformin, it was found that when used with chemotherapeutic agents or inhibitors used in lung cancer, better treatment response and fewer side effects were obtained. This was supported by Sayed et al.[56] analyses of non-small cell lung cancers in the fourth stage.

Metformin added to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), which is the current therapy for EGFR mutation-positive non-small cell lung cancer, has been found that extend survival and slow cancer progression as molecular lower levels are decreased.[57]

METFORMIN AND OTHER TYPES OF CANCERS

The enlightenment of metformin's energy pathways and the observation of its anti-cancer effects, together with the accumulated analysis, have created a curiosity in many types of cancer. In addition to colorectal, lung, gynecological, and breast cancers, metformin also has anti-cancer effects in the pancreas, gastric, esophagus, and other types of cancers.[58]

Chronic pancreatitis is a contemporary cause of pancreatic cancer development. In rats with chronic pancreatitis, metformin was reported to reduce the development of pancreatic cancer, inhibit tumor formation, and prevent the formation of pancreatic ductal adenocarcinoma (PDAC).[59] Metformin decreased fibrosis and metaplasia caused by chronic pancreatitis in genetically modified mice PDAC models, according to this study. Furthermore, metformin lowered tumor burden and increased overall survival.

A study investigating the effects of metformin on gastric cancer confirmed its antitumor effects. Gastric cancer stem cells such as MK45, AGS, and MKN74 obtained from the cancer cell line were examined *in vitro*, and in *in vivo* mouse models, tumor cells derived from the patient were examined in different dimensions. The study's findings have resulted in a decrease in cancer stem cell proliferation, stagnation in the cell cycle, and a delay in tumor growth.[60]

In research on the effect of metformin on esophageal cancers, significant improvements were seen in esophageal squamous cell carcinoma (ESCC) resistant to chemotherapy and radiotherapy, escaping apoptosis. In an *in vitro* study, treatment with metformin was associated with a higher response to chemotherapy and radiotherapy.[61]

The increasing incidence of cancer in the world and the inadequacy of available treatments have led to the search for effective solutions to cancer. One of these ways is to illuminate the tumor energy pathways. Meta-analyses and systematic reviews have shown that metformin is both an inexpensive and easily available agent and may be effective against some types of cancer.[34,47,55]

Metformin studies, which started with the increased incidence of cancer in T2DM patients[5], showed the beneficial effects of metformin against cancer, and its effects on the mechanism at the cellular and systemic levels were shown. This situation, which is supported by *in vivo* and *in vitro* studies, can be given as an example of the indispensable anti-cancer effects of halting the reproduction of cells in the tumoral line, inducing apoptosis, as in colorectal cancer[27] and lung cancers.[51,52]

Decreased cancer rates in individuals using metformin, supported by extensive retrospective studies and field analyses, again supported the anti-cancer effect, and increased chemo-radiotherapy response in those using metformin in studies conducted with cancer patients made this situation effectively.[23,32,48]

In view of all these situations, the issue of adding metformin to adjuvant or non-adjuvant therapy in patients with a high risk of developing diabetic or

non-diabetic cancer and in patients diagnosed with cancer may come up and should be evaluated.

In conclusion, metformin is a therapeutic agent that is mostly used in T2DM. Recent findings and observations of anti-cancer properties in many types of cancer have made this agent a valuable study subject. Particularly, in studies conducted by elucidating the energy pathways of cancer cells today, AMPK activation and inhibition of mTOR signal at the cellular level; autophagy, and apoptosis in tumor cells supported the anti-tumor effects of metformin. Inhibiting molecules that mediate cell migration as in colorectal cancers, positive effects on lipid and steroid metabolism in breast cancers, activation of important tumor suppressors such as p53 in gynecological cancers, and targeting cells in the lung and other cancer cell lines, are the tremendous effects of metformin on human cancers. The advantages of metformin on many tumors have been demonstrated in clinical trials, as well as the high response is given with medicines such as other combined chemotherapy. All this information could make metformin a potential new cancer target. Metformin has the potential to be a therapeutic option for many types of cancer; however, further clinical research is needed.

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REFERENCES

1. World Health Organization. WHO model list of essential medicines. 2015. Available from: www.who.int/medicines/publications/
2. Bailey CJ. Metformin: historical overview. Diabetologia. 2017 Sep;60:1566-76.
3. Erbas O, Taşkıran D, Oltulu F, Yavaşoğlu A, Bora S, Bilge O, Çınar BP, Peker G. Oxytocin provides protection against diabetic polyneuropathy in rats. Neurol Res. 2017 Jan;39:45-53.
4. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015 Mar;31:196-201.
5. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med. 2016 Jun 7;164:740-51.
6. Flory J, Lipska K. Metformin in 2019. JAMA. 2019 May 21;321:1926-27.
7. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci. 2014 Jul;19:658-64.
8. Chen K, Li Y, Guo Z, Zeng Y, Zhang W, Wang H. Metformin: current clinical applications in nondiabetic patients with cancer. Aging (Albany NY). 2020 Feb 18;12:3993-4009.
9. 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 Care. 2009 Sep;32:1620-5
10. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab. 2014 Dec 2;20:953-66.
11. Correia S, Carvalho C, Santos MS, Seiça R, Oliveira CR, Moreira PI. Mechanisms of action of metformin in type 2 diabetes and associated complications: an overview. Mini Rev Med Chem. 2008 Nov;8:1343-54.
12. Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J. 2000 Jun 15;348 Pt 3:607-14.
13. Anisimov VN, Bartke A. The key role of growth hormone-insulin-IGF-1 signaling in aging and cancer. Crit Rev Oncol Hematol. 2013 Sep;87:201-23.
14. Stephenne X, Foretz M, Taleux N, van der Zon GC, Sokal E, Hue L, et al. Metformin activates AMP-activated protein kinase in primary human hepatocytes by decreasing cellular energy status. Diabetologia. 2011 Dec;54:3101-10.
15. Murugan AK. mTOR: Role in cancer, metastasis and drug resistance. Semin Cancer Biol. 2019 Dec;59:92-111.
16. Atasoy Ö, Erbaş O. Up to date of prostate cancer. D J Med Sci 2020;6:92-102.
17. Wheaton WW, Weinberg SE, Hamanaka RB, Soberanes S, Sullivan LB, Anso E, et al. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. Elife. 2014 May 13;3:e02242.
18. Atasoy O, Cini N, Erdogan MA, Yaprak G, Erbas O. Radiotherapy and high bilirubin may be metformin like effect on lung cancer via possible AMPK pathway modulation. Bratisl Lek Listy. 2022;123:100-9.
19. Beck E, Scheen AJ. La metformine: une molécule antidiabétique dotée de propriétés anti-cancéreuses [Metformin, an antidiabetic molecule with anti-cancer properties]. Rev Med Liège. 2013 Sep;68:444-9. French.
20. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One. 2012;7:e33411
21. Yu X, Mao W, Zhai Y, Tong C, Liu M, Ma L, et al. Anti-tumor activity of metformin: from metabolic and epigenetic perspectives. Oncotarget. 2017 Jan 17;8:5619-28.
22. Weitz J, Koch M, Debus J, Höhler T, Galle PR, Büchler MW. Colorectal cancer. Lancet. 2005 Jan 8-14;365:153-65.
23. Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2020 Jul;70:313.

24. Ulucutsoy B, Çini N, Erbaş O. Microsatellite Instability in Lynch Syndrome and Colorectal Cancers. JEB Med Sci 2021;2:375-9.
25. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology. 2004 Oct;127:1044-50.
26. 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). 2008 Oct;1:369-75
27. Zhou XZ, Xue YM, Zhu B, Sha JP. [Effects of metformin on proliferation of human colon carcinoma cell line SW-480]. Nan Fang Yi Ke Da Xue Xue Bao. 2010 Aug;30:1935-8,1942. Chinese.
28. Sabit H, Abdel-Ghany SE, M Said OA, Mostafa MA, El-Zawahry M. Metformin Reshapes the Methylation Profile in Breast and Colorectal Cancer Cells. Asian Pac J Cancer Prev. 2018 Oct 29;19:2991-9
29. Sevinç S, Erbaş O. Effects of DNA Methylation on Cancer and Aging. JEB Med Sci 2020;1:126-30.
30. Rennert G, Rennert HS, Gronich N, Pinchev M, Gruber SB. Use of metformin and risk of breast and colorectal cancer. Diabetes Res Clin Pract. 2020 Jul;165:108232.
31. Budh DP, Sapra A. Cancer Breast Screening. 2021 Feb 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan
32. Samuel SM, Varghese E, Kubatka P, Triggle CR, Büsselberg D. Metformin: The Answer to Cancer in a Flower? Current Knowledge and Future Prospects of Metformin as an Anti-Cancer Agent in Breast Cancer. Biomolecules. 2019 Dec 9;9:846.
33. Yürekli A, Erbaş O. Cancer and Immunosuppression. JEB Med Sci 2021;2:116-21.
34. Tang GH, Satkunam M, Pond GR, Steinberg GR, Blandino G, Schünemann HJ, et al. Association of Metformin with Breast Cancer Incidence and Mortality in Patients with Type II Diabetes: A GRADE-Assessed Systematic Review and Meta-analysis. Cancer Epidemiol Biomarkers Prev. 2018 Jun;27:627-35.
35. Xu H, Chen K, Jia X, Tian Y, Dai Y, Li D, et al. Metformin Use Is Associated With Better Survival of Breast Cancer Patients With Diabetes: A Meta-Analysis. Oncologist. 2015 Nov;20:1236-44.
36. Faria J, Negalha G, Azevedo A, Martel F. Metformin and Breast Cancer: Molecular Targets. J Mammary Gland Biol Neoplasia. 2019 Jun;24:111-23.
37. Wysocki PJ, Wierusz-Wysocka B. Obesity, hyperinsulinemia and breast cancer: novel targets and a novel role for metformin. Expert Rev Mol Diagn. 2010 May;10:509-19.
38. Hatoum D, McGowan EM. Recent advances in the use of metformin: can treating diabetes prevent breast cancer? Biomed Res Int. 2015;2015:548436.
39. Wahdan-Alaswad RS, Edgerton SM, Salem HS, Thor AD. Metformin Targets Glucose Metabolism in Triple Negative Breast Cancer. J Oncol Transl Res. 2018;4:129.
40. Park YM, Bookwalter DB, O'Brien KM, Jackson CL, Weinberg CR, Sandler DP. A prospective study of type 2 diabetes, metformin use, and risk of breast cancer. Ann Oncol. 2021 Mar;32:351-59.
41. Rayburn WF. Gynecologic Cancer Care: Innovative Progress. Obstet Gynecol Clin North Am. 2019 Mar;46:xiii-xiv.
42. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Polycystic ovary syndrome. Nat Rev Dis Primers. 2016 Aug 11;2:16057.
43. Meczekalski B, Pérez-Roncero GR, López-Baena MT, Chedraui P, Pérez-López FR. The polycystic ovary syndrome and gynecological cancer risk. Gynecol Endocrinol. 2020 Apr;36:289-93.
44. Chen YH, Yang SF, Yang CK, Tsai HD, Chen TH, Chou MC, et al. Metformin induces apoptosis and inhibits migration by activating the AMPK/p53 axis and suppressing PI3K/AKT signaling in human cervical cancer cells. Mol Med Rep. 2021 Jan;23:88.
45. Du WW, Fang L, Yang W, Wu N, Awan FM, Yang Z, et al. Induction of tumor apoptosis through a circular RNA enhancing Foxo3 activity. Cell Death Differ. 2017 Feb;24:357-70.
46. Hu T, Chung YM, Guan M, Ma M, Ma J, Berek JS, et al. Reprogramming ovarian and breast cancer cells into non-cancerous cells by low-dose metformin or SN-38 through FOXO3 activation. Sci Rep. 2014 Jul 24;4:5810.
47. Meireles CG, Pereira SA, Valadares LP, Rêgo DF, Simeoni LA, Guerra ENS, et al. Effects of metformin on endometrial cancer: Systematic review and meta-analysis. Gynecol Oncol. 2017 Oct;147:167-80.
48. Gadducci A, Biglia N, Tana R, Cosio S, Gallo M. Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning. Crit Rev Oncol Hematol. 2016 Sep;105:73-83.
49. Ko EM, Walter P, Jackson A, Clark L, Franasiak J, Bolac C, et al. Metformin is associated with improved survival in endometrial cancer. Gynecol Oncol. 2014 Feb;132:438-42
50. Wen Q, Zhao Z, Wen J, Zhou J, Wu J, Lei S, Miao Y. The association between metformin therapy and risk of gynecological cancer in patients: Two meta-analyses. Eur J Obstet Gynecol Reprod Biol. 2019 Jun;237:33-41.
51. Ashinuma H, Takiguchi Y, Kitazono S, Kitazono-Saitoh M, Kitamura A, Chiba T, et al. Antiproliferative action of metformin in human lung cancer cell lines. Oncol Rep. 2012 Jul;28:8-14.
52. Wang J, Gao Q, Wang D, Wang Z, Hu C. Metformin inhibits growth of lung adenocarcinoma cells by inducing apoptosis via the mitochondria-mediated pathway. Oncol Lett. 2015 Sep;10:1343-49.
53. Ma Y, Guo FC, Wang W, Shi HS, Li D, Wang YS. K-ras gene mutation as a predictor of cancer cell responsiveness to metformin. Mol Med Rep. 2013 Sep;8:763-8.
54. Groenendijk FH, Mellema WW, van der Burg E, Schut E, Hauptmann M, Horlings HM, et al. Sorafenib synergizes with metformin in NSCLC through AMPK pathway activation. Int J Cancer. 2015 Mart 15;136:1434-44.
55. Yao L, Liu M, Huang Y, Wu K, Huang X, Zhao Y, et al. Metformin Use and Lung Cancer Risk in Diabetic Patients: A Systematic Review and Meta-Analysis. Dis Markers.

2019 Feb 10;2019:6230162.

56. Sayed R, Saad AS, El Wakeel L, Elkholy E, Badary O. Metformin Addition to Chemotherapy in Stage IV Non-Small Cell Lung Cancer: an Open Label Randomized Controlled Study. Asian Pac J Cancer Prev. 2015;16:6621-6.
57. Arrieta O, Barrón F, Padilla MS, Avilés-Salas A, Ramírez-Tirado LA, Arguelles Jiménez MJ, et al. Effect of Metformin Plus Tyrosine Kinase Inhibitors Compared With Tyrosine Kinase Inhibitors Alone in Patients With Epidermal Growth Factor Receptor-Mutated Lung Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019 Nov 1;5:e192553
58. Vancura A, Bu P, Bhagwat M, Zeng J, Vancurova I. Metformin as an Anticancer Agent. Trends Pharmacol Sci. 2018 Oct;39:867-78.
59. Chen K, Qian W, Jiang Z, Cheng L, Li J, Sun L, et al. Metformin suppresses cancer initiation and progression in genetic mouse models of pancreatic cancer. Mol Cancer. 2017 July 24;16:131.
60. Courtois S, Durán RV, Giraud J, Sifré E, Izotte J, Mégraud F, et al. Metformin targets gastric cancer stem cells. Eur J Cancer. 2017 Oct;84:193-201.
61. Wang L, Li K, Lin X, Yao Z, Wang S, Xiong X, et al. Metformin induces human esophageal carcinoma cell pyroptosis by targeting the miR-497/PELP1 axis. Cancer Lett. 2019 May 28;450:22-31.