Research Article

Study of the Association Between Antihyperglycemic Therapy and Cancer in Patients with Type 2 Diabetes Mellitus

Tamara Vatseba[1*], Liubov Sokolova[2], Volodymyr Pushkarev[2], Nataliia Koshel[3]

Abstract

The objective of the research was to investigate the features and association of antihyperglycemic therapy and cancer in patients with type 2 diabetes mellitus.

Materials and Methods. The study included the analysis of medical records of patients with type 2 diabetes mellitus who were diagnosed with cancer during 2012-2016. The obtained results were processed by statistical methods using the software packages Microsoft Excel and Statistika-12. The significance of differences between the frequency of using different treatment schemes was assessed by the Pearson's test (χ^2). To determine the risk of predicted events, the odds ratio, the 95% confidence interval, the positive and negative prognostic values were calculated.

Results. There were diagnosed 533 cases of cancer in patients with type 2 diabetes mellitus. The most common scheme of antihyperglycemic therapy prior to the detection of malignant diseases was a combination of metformin and sulfonylurea derivatives (35.65%), as well as monotherapy with sulfonylurea derivatives (17.26%) and metformin (11.28%). Prior to diagnosing cancer in 396 (74.30%) patients, antihyperglycemic therapy that included sulfonylurea derivates or insulin was used. Among obese patients 68.82% used sulfonylureas and insulin as part of antidiabetic therapy before diagnosis of cancer. The connection between insulin therapy and the risk of cancer development in patients with type 2 diabetes mellitus was proved (the odds ratio=2.35; the 95% confidence interval (1.91 - 2.91); p < 0.001).

Conclusions. Prior to the detection of cancer in patients with type 2 diabetes mellitus, the combination therapy with metformin and sulfonylurea derivatives was most often used. The association between insulin therapy and the development of cancer in patients with type 2 diabetes mellitus was revealed. Cancer screening is advisable for patients with type 2 diabetes mellitus and obesity, who receive as a therapy sulfonylurea derivates and/or insulin.

Keywords

antihyperglycemic therapy; cancer; association

[1] *Ivano-Frankivsk National Medical University, Ukraine.*

[2] *V.P. Komisarenko Institute of Endocrinology and Metabolism, National Academy of Medical Sciences of Ukraine, Ukraine.*

[3] *D.F. Chebotarev Institute of Gerontology, National Academy of Medical Sciences of Ukraine, Ukraine.*

*Corresponding author: tamara.vatseba@gmail.com

Problem statement and analysis of the latest research

The increased risk of cancer in patients with diabetes mellitus (DM) encourages scientists to study the mechanisms of association between the two pathologies. Hyperinsulinemia and hyperglycemia are recognized as the main pathogenetic factors of cancer in patients with DM [1]. Chronic exposure to these factors disrupts the activity of regulatory systems of cellular activity, metabolism and survival.

In type 2 DM (T2DM) and obesity, hyperinsulinemia and constant nutritional excess cause hyperactivity of anabolism, protein synthesis, which can cause disorders of the cell cycle at different stages, contributing to the influence of oncogenes on the proliferation and apoptosis processes.

Hyperglycemia contributes to oncogenesis through indirect and direct procarcinogenic effects. The indirect effect is caused by the stimulation of certain organs to the synthesis of growth factors (insulin / insulin-like growth factor – IGF-1) and pro-inflammatory cytokines. The direct effect is the induction of mutations in the cell due to oxidative stress (OS) and activation of signaling pathways associated with carcinogenesis.

Under physiological conditions, the processes of metabolism, proliferation, and apoptosis are controlled by the coordinated interaction of many signaling systems, the activity of which depends on the influence of factors of their activation and inhibition. One of the most important signaling pathways involved in the regulation of oncogenesis and metabolism in diabetes is the PI3K/Akt/mTORC1 pathway, the main components of which are phosphoinositide-3-kinase (PI3K), Akt kinase (Protein kinase B alpha) and mTOR (mechanistic target of rapamycin kinase) [2]. Activating factors of PI3K/Akt/mTORC1 are insulin and IGF-1, the level of which in DM is often increased due to insulin resistance and hyperinsulinemia (endogenous and exogenous) [3].

MTORC1 is a key kinase of this pathway, which regulates the processes of cell proliferation, apoptosis, and metabolism through its effect on the ribosomal protein kinase p70S6K and protein synthesis. The physiological inhibitor of mTORC1 activity is an activated adenosine monophosphate protein kinase (AMPK), which, if necessary, causes the reorganization of cellular metabolism to the mode necessary to restore energy balance in the cell [4]. However, under conditions of prolonged nutrient and energy overload in T2DM, AMPK function may be insufficient.

The chronic clinical course of DM and the need for continuous daily treatment led to a sound scientific study of possible mechanisms of association of the two diseases through the influence of antihyperglycemic therapy (AHGT).

Due to the progressive development of scientific and practical medicine, nowadays, diabetics have access to a wide range of antihyperglycemic drugs (AHGD) with different mechanisms of action, which are taken into account when choosing a treatment for patients at different stages of DM, considering insulin-producing capacity of the pancreas, side effects and accompanying diseases in each individual case.

Patients with type 1 DM are known to require insulin replacement therapy, and patients with T2DM traditionally start their therapy with AHGD in tablet form, however, with time, many of them require treatment with insulin either.

To date, different types of insulin and tablet AHGD of high-quality are available for patients. According to the mechanism of action, tablet antidiabetic drugs are divided into:

1. Insulin sensitizers (biguanides and thiazolidinediones);

2. Secretagogues: sulfonylurea derivatives (SUD) and benzoic acid derivatives;

3. Stimulators of incretin hormones activity (incretinomimetics): glucagon-like peptide-1 analogues (aGLP-1) and dipeptidylpeptidase-4 inhibitors (iDPP-4);

4. Drugs that inhibit the absorption of glucose into the blood through the intestine (α-glucosidase inhibitors);

5. Drugs that block the reabsorption of glucose by the kidneys (sodium-glucose co-transporter-2 (SGLT2) inhibitors).

Given the ability of AHGD to lower blood glucose levels, it is natural and obvious that all groups of antidiabetic drugs inhibit the processes of carcinogenesis caused by hyperglycemia. On the other hand, different mechanisms of action of drugs cause additional pleiotropic effects due to their modifying effect on other diabetes-dependent cancer risk factors.

Metformin, which is the drug of choice in the treatment of patients with T2DM, has the best oncoprotective properties. Recent studies have shown that metformin therapy reduces the risk of cancer of the lungs [5], colorectal localization [6], ovaries [7], mammary glands [8], and endometrium [9].

SUD currently dominate among second-line drugs for the treatment of patients with T2DM owing to their affordability and potent hypoglycemic effect, including people with oncological diseases [10]. Studies proved the prooncogenic effect of drugs in this group due to the effects of hyperinsulinemia [11, 12]. The role of iatrogenic hyperinsulinemia (as a result of insulin therapy) as a factor of oncogenesis has been proven in many studies [13], but the results of some studies differ [14].

The objective of the research was to investigate the features and association of antihyperglycemic therapy and cancer in patients with T2DM.

1. Materials and Methods

The study was conducted in accordance with the guidelines of the Declaration of Helsinki 1975 and its revised 1983 version. The research was carried out on the basis of the analysis of medical records of inpatients and outpatients with T2D who were diagnosed with cancer during 2012-2016. The bases for the study were: the Precarpathian Oncology Center, the Ivano-Frankivsk Regional Clinical Hospital, medical institutions of Ivano-Frankivsk region. The obtained results were processed by statistical methods in the software packages Microsoft Excel and Statistika-12.

The significance of the difference between the frequency of using different treatment regimens was assessed by the Pearson's test (χ^2). To determine the risk of predicted events, the odds ratio (Odds-ratio, OR), the 95% confidence interval (CI), the positive and negative prognostic values were calculated.

Ethics Policy

The study is a fragment of the research project "Epidemiology of Oncological Diseases in Patients with Diabetes Mellitus and the Effect of Antihyperglycemic Drugs on Oncogenesis Markers" (registration number 0117U005263), included into the complex research work of the Ivano-Frankivsk National Medical University "Pathogenetic Mechanisms of Development of Changes in Organs of the Respiratory, Endocrine, Nervous Systems in the Modeled Pathological Conditions and Their Correction" (registration number 0117U001758), without special funding.

The study protocol was reviewed and approved by the Ethics Committee of the Ivano-Frankivsk National Medical University (protocol No 97/17 of October 19, 2017).

2. Results and Discussion

According to the processed archival data, during 2012-2016, 533 cases of cancer were diagnosed in patients with T2DM. The most common localizations of malignant neoplasms (MN) are presented in Fig. 1.

MN of other localizations were diagnosed in 46 patients with a low frequency, in particular lymphatic system cancer was detected with the frequency of every localization case less than 1.5%: the incidence of thyroid cancer was 1.13%, the brain – 0.94%, biliary tract, female external genitalia (EG), nasal sinuses – 0.75%, soft tissues and parotid salivary glands – 0.56%, esophagus and oropharynx – 0.38%, bones, adrenal glands, urinary tract, small intestine, male EG – 0.19%.

In accordance with the objective of the study, the analysis of AHGT in patients with T2DM prior to the detection of cancer was carried out (Table 1).
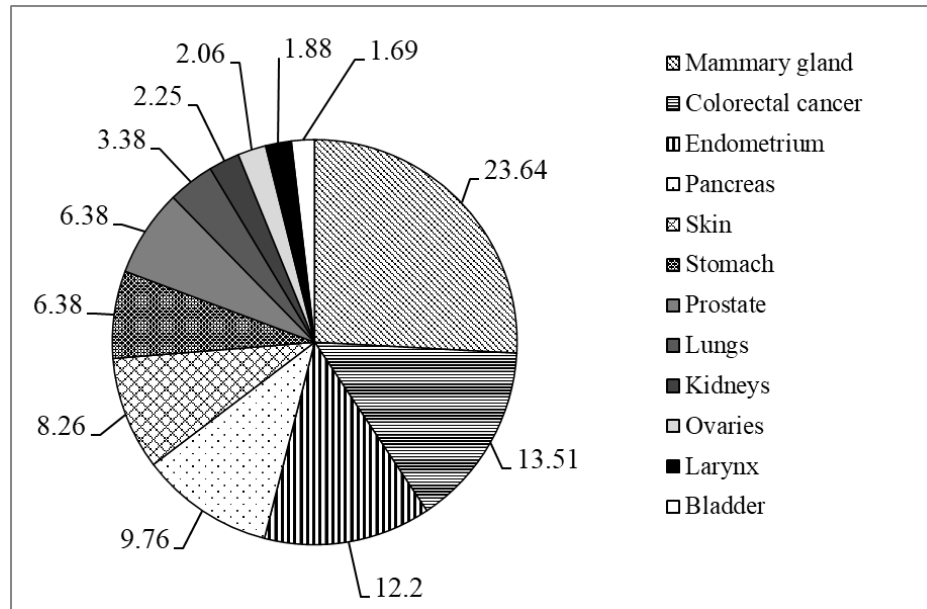
Figure 1. MN of the most widespread localizations in patients with T2DM (n=487).
Note: % – percentage of the total number of MN cases.

Table 1. AHGT of patients with T2DM prior to the detection of cancer.

Therapy	Number of patients (n=533)	Frequency (%)
Diet	60	11.26
Metformin (monotherapy)	63	11.82
Metformin + iDPP-4	9	1.69
Metformin + glitazones	1	0.19
Metformin + SGLT2 inhibitors	2	0.38
Metformin + SUD	190	35.65
Metformin + insulin	49	9.19
Glitazones (monotherapy)	2	0.38
SUD (monotherapy)	92	17.26
Insulin (monotherapy)	56	10.51
Metformin + iDPP-4 + insulin	1	0.19
Metformin + iDPP-4 + SUD	2	0.38
SUD + insulin	6	1.13

According to the results shown in Table 1, the most common treatment scheme for patients with T2DM prior to the detection of cancer was a combination of metformin and SUD. This scheme is traditionally used in the treatment of patients with T2DM.

A comparative analysis of the number of patients who used insulin preparations and SUD as part of AHGT before the detection of cancer was carried out (Fig. 2).

These groups of AHGD in daily therapy were found to be taken by 396 patients with T2DM; 137 patients used other groups of antidiabetic agents, without insulin or SUD.
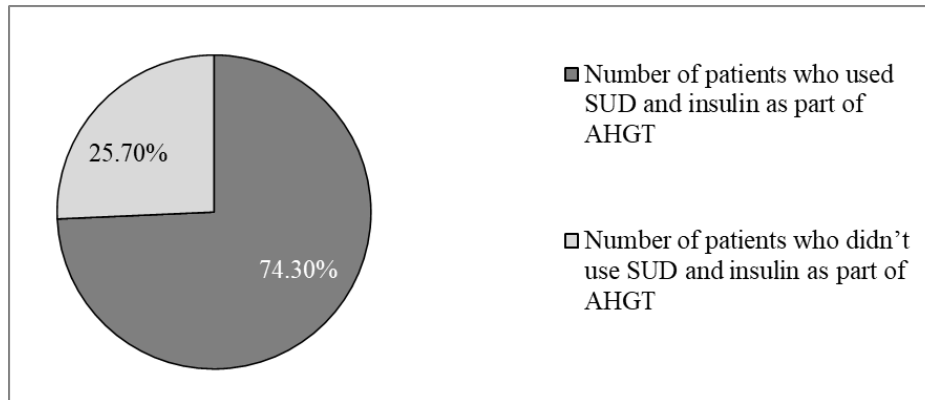
Figure 2. Frequency of using SU and insulin drugs as part of AHGT by patients with T2DM prior to the detection of cancer.

Note: % – percentage of the total number of patients with MN (n=533).

Frequent use of these drugs, obviously, has its own explanation in each individual case. Traditionally and naturally, secretagogues and insulin replacement therapy are prescribed to patients with insulin deficiency, or in case of contraindications to AHGD of other groups.

According to the processed data, 279 (52.35%) patients suffered from obesity with a body mass index (BMI) > 30 kg/m^2, 254 (47.65%) patients were not obese.

The analysis of the frequency of using these groups of drugs in obese patients was carried out (Table 2).

Statistical analysis showed a significantly higher frequency of using AHGT that included insulin and/or secretagogues in non-obese patients with T2DM (P ¡ 0.05). However, it was found that among 279 obese patients,192 patients (68.82%) received these schemes of treatment (Table 2).

The data obtained confirmed the frequent use of insulin drugs and SUD in the schemes of AHGT, including obese patients, which might contribute to hyperinsulinemia. Based on the archival data studied, we cannot reliably confirm the presence of hyperinsulinemia (since insulin levels were not determined); however, taking into account the value of BMI (as a sign of insulin resistance), this assumption may be correct.

According to official data presented in the state statistical reporting form No 12 "Report on Diseases Registered in Patients Living in the Area of Treatment and Prevention Facilities" in Ivano-Frankivsk region during 2012-2016, 42,532 patients with T2DM were registered; among them, 4,376 people were on insulin therapy, 38,156 patients did not use insulin.

The analysis of the impact of insulin therapy on the risk of cancer was performed (Table 3).

Patients with T2DM who use insulin as part of AHGT were found to have twice the risk of cancer as compared to patients on other treatment regimens. In this case, it is impossible to state categorically about the direct impact of insulin therapy on the development of cancer, as this statement requires the additional data, in particular on the duration of insulin therapy before diagnosing cancer, which is often not mentioned in patient documentation used for epidemiological research. A comparative analysis of cancer risk in patients with other AHGT schemes would also be appropriate. However, the lack of a register of patients with T2DM who use tablet AHGD does not allow determining the risk of cancer associated with the use of other groups of antidiabetic drugs.

To date, metformin has the most obvious anti-tumor activity due to its ability to reduce insulin resistance and hyperinsulinemia. At the molecular level, metformin, by activating AMPK, affects the activity of the PI3K/Akt/mTOR signaling pathway [1, 15].

Table 2. Use of SU derivatives and insulin in patients with diabetes and cancer

Total number of obese patients (n=279)		Total number of patients without obesity (n=254)		χ^2	p
Treated with insulin and SUD as part of AHGT	Without insulin and SUD as part of AHGT	Treated with insulin and SUD as part of AHGT	Without insulin and SUD as part of AHGT		
192	87	205	49	9.28	0.002

Table 3. The risk of cancer in patients with T2DM is associated with insulin therapy.

Total number of cancer patients	Number of patients with T2DM treated with insulin therapy		Number of patients with T2DM treated without insulin therapy		OR	95% CI	p
	Total	With MN	Total	With MN			
533	4376	112	38156	421	2.35	1.91 - 2.91	p<0.001

In contrast to metformin, the property of SUD to stimulate insulin synthesis by β-cells of the pancreas explains the possible prooncogenic effect of these drugs through the effects of hyperinsulinemia and the activation of signaling pathways involved in carcinogenesis. The studies have proven this effect [12, 16].

However, according to a comparative meta-analysis of many studies, the risk of cancer in patients taking SUD is ambiguous and depends on the generation of drugs, their affinity with receptors of the pancreas and differentiated insulin exposition [14].

Recent studies have proven the potential onco-protective properties of SUD, which are associated with inhibition of vascular endothelial growth factor (VEGF), which inhibits the neovascularization of MN and the invasiveness of cancer cells. Chlorpropamide has been shown to have a selective ability to inhibit Akt pathway activity in cancer cells, leading to cell growth arrest and apoptosis of cancer cells in vitro and in vivo. In addition, SUD reduce the level of TNF-α and the number of TNF-α receptors in cancer cells, having a beneficial effect on the tumor microenvironment. It has been also proven that drugs of this group have antioxidant effect, which is due to their effect on ATP-dependent K+channels and activation of antioxidant systems of the body that can inhibit cell growth by inducing apoptosis [14, 17]. These effects can be very useful in the treatment of cancer, but only for those who have no hyperinsulinemia.

Numerous scientific studies have presented a large evidence base of hyperinsulinemia as a factor of oncogenesis, including the organs of the reproductive system, pancreas and large intestine [18, 19].

Insulin activates the processes of oncogenesis in several ways. One of the mechanisms is associated with the activation of the PI3K/Akt/mTOR signaling pathway both through its own insulin receptors (IR) and through IGF-1R, as hyperinsulinemia reduces the level of the protein that binds IGF-1, increasing the bioavailability of the latter.

On the other hand, early initiation of insulin therapy or insulin therapy in doses higher than physiological ones, stimulate lipogenesis, lead to increased BMI, causing insulin resistance, hyperinsulinemia, hyperglycemia, and chronic inflammation [20].

In the treatment of patients with T2DM with obesity or overweight, it is often impossible to achieve physiological insulin concentrations by exogenous administration, as insulin resistance requires high doses of insulin, and therefore, insulin therapy itself promotes secondary insulin resistance,

forming a vicious circle favorable to neoplasia [20].

It is reasonable to study the effect of insulin analogues on carcinogenesis, as these types of insulin have 6-8 times higher affinity for binding to IGF-1R than human insulin [21]. Recent studies and meta-analyzes have not confirmed a significant effect of insulin analogues on oncogenesis [22, 23].

The conducted epidemiological analysis included cases of cancer in patients with DM of the 5-year period during 2012-2016, when the latest AHGD with extrapancreatic mechanisms of action have not become widely used yet. SUD and insulin drugs are currently widely used as AHGT of the second- and third-line therapy for patients with T2DM. This choice is often made due to the unavailability (the high price) of the latest drugs that reduce hyperglycemia without early stimulation of insulin synthesis, and they also have the ability to prevent serious complications of DM, including the ability to improve the weight of patients. These data may be useful in the choice of AHGT for patients with T2DM, taking into account the negative impact of hyperinsulinemia (endogenous and exogenous), as well as obesity on the processes of oncogenesis. Before prescribing drugs that raise blood insulin levels, it is advisable to assess the insulin-producing reserves of the pancreas and the presence of insulin resistance to prevent hyperinsulinemia with a view to cancer prevention.

3. Conclusions

1. Prior to the detection of cancer in patients with T2DM, combination therapy with metformin and sulfonylurea derivatives was most often used.
2. The association between insulin therapy and the development of cancer in patients with T2DM was revealed.
3. For obese patients with T2DM, who receive sulfonylurea derivatives and/or insulin, cancer screening is advisable.

Conflict of Interest

The authors stated no conflict of interest.

Financial Disclosure

References

[1] Pushkarev VM, Sokolova LK, Pushkarev VV et al. Biochemical mechanisms connecting diabetes and cancer. Effects of methormine. Endocrinology. 2018; 23 (2): 167-179. [published in Russian]

[2] Manning BD, Toker A. AKT/PKB Signaling: Navigating the Network. Cell. 2017; 169 (3): 381-405. DOI: https://doi.org/10.1016/j.cell.2017.04.001 [PMid:28431241 PMCid:PMC5546324]

[3] Vatseba TS. The role of insulin, IGF-1 and PRAS40 in the processes of oncogenesis in women with diabetes mellitus type 2 and endometrial cancer. Galician Medical Journal. 2019; 26 (4): 7-11. DOI: https://doi.org/10.21802/gmj.2019.4.7

[4] Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol. 2011; 12 (1): 21-35. DOI: https://doi.org/10.1038/nrm3025 [PMid:21157483 PMCid:PMC3390257]

[5] Yao L, Liu M, Huang Y et al. Metformin Use and Lung Cancer Risk in Diabetic Patients: A Systematic Review and Meta-Analysis. Dis Markers. 2019; 6230162. DOI: https://doi.org/10.1155/2019/6230162 [PMid:30881522 PMCid:PMC6387718]

[6] Liu F, Yan L, Wang Z et al. Metformin therapy and risk of colorectal adenomas and colorectal cancer in type 2 diabetes mellitus patients: A systematic review and meta-analysis. Oncotarget. 2017; 8 (9): 16017-16026. DOI: https://doi.org/10.18632/oncotarget.13762 [PMid:27926481 PMCid:PMC5362542]

[7] Tseng CH. Metformin reduces ovarian cancer risk in Taiwanese women with type 2 diabetes mellitus. Diabetes Metab Res Rev. 2015; 31 (6): 619-626. DOI: https://doi.org/10.1002/dmrr.2649 [PMid:25820555]

[8] Tseng CH. Metformin may reduce breast cancer risk in Taiwanese women with type 2 diabetes. Breast Cancer Res Treat. 2014; 145 (3): 785-790. DOI: https://doi.org/10.1007/s10549-014-2985-8 [PMid:24816805]

[9] Tian J, Liang Y, Qu P. Antidiabetic Medications and the Risk of Endometrial Cancer in Patients. Gynecol Obstet Invest 2019; 84: 455-462. DOI: https://doi.org/10.1159/000497202 [PMid:30808843]

[10] Vatseba TS. Cancer of the organs of the reproductive system in women with type 2 diabetes. Effects of antidiabetic therapy. Wiadomości Lekarskie. 2020;73(5): 967-971.

[11] Mekuria AN, Ayele Y, Tola A et al. Monotherapy with Metformin versus Sulfonylureas and Risk of Cancer in Type 2 Diabetic Patients: A Systematic Review and Meta-Analysis. J Diabetes Res. 2019; 7676909. DOI: https://doi.org/10.1155/2019/7676909 [PMid:31828167 PMCid:PMC6885827]

[12] Dabrowski M, Szymańska-Garbacz E, Miszczyszyn Z et al. Antidiabetic medications use and cancer risk in type 2 diabetes. Clinical Diabetology. 2017; 6 (1): 17-25. DOI: https://doi.org/10.5603/DK.2017.0004

[13] Colmers IN, Bowker SL, Tjosvold LA et al. Insulin use and cancer risk in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies. Diabetes Metab. 2012; 38 (6): 485-506. DOI: https://doi.org/10.1016/j.diabet.2012.08.011 [PMid:23159131]

[14] Hendriks AM, Schrijnders D, Kleefstra N et al. Sulfonylurea derivatives and cancer, friend or foe?. Eur J Pharmacol. 2019; 861: 172598. DOI: https://doi.org/10.1016/j.ejphar.2019.172598 [PMid:31408647]

[15] Song CW, Lee H, Dings RP et al. Metformin kills and radiosensitizes cancer cells and preferentially kills cancer stem cells. Sci Rep. 2012; 2: 362. DOI: https://doi.org/10.1038/srep00362 [PMid:22500211 PMCid:PMC3324825]

[16] Thakkar B, Aronis KN, Vamvini MT et al. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism. 2013; 62 (7): 922-934. DOI: https://doi.org/10.1016/j.metabol.2013.01.014 [PMid:23419783]

[17] Pasello G, Urso L, Conte P et al. Effects of sulfonylureas on tumor growth: a review of the literature. Oncologist. 2013; 18 (10): 1118-1125. DOI: https://doi.org/10.1634/theoncologist.2013-0177 [PMid:24043597 PMCid:PMC3805154]

[18] Call R, Grimsley M, Cadwallader L et al. Insulin–carcinogen or mitogen? Preclinical and clinical evidence from prostate, breast, pancreatic, and colorectal cancer research. Postgrad Med. 2010; 122 (3): 158-165. DOI: https://doi.org/10.3810/pgm.2010.05.2153 [PMid:20463425]

[19] Singh S, Singh H, Singh PP et al. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2013; 22 (12): 2258-2268. DOI: https://doi.org/10.1158/1055-9965.EPI-13-0429 [PMid:24042261]

[20] Tseng CH. Prolonged use of human insulin increases breast cancer risk in Taiwanese women with type 2 diabetes. BMC Cancer. 2015; 15: 846. DOI: https://doi.

org/10.1186/s12885-015-1876-7
[PMid:26537234 PMCid:PMC4632264]

[21] Kurtzhals P, Schä ffer L, Sø rensen A et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes. 2000; 49 (6): 999-1005. DOI: https://doi.org/10.2337/diabetes.49.6.999 [PMid:10866053]

[22] Grimaldi-Bensouda L, Cameron D, Marty M et al. ISICA Group. Risk of breast cancer by individual insulin use: an international multicenter study. Diabetes Care. 2014; 37 (1): 134-143. DOI: https://doi.org/10.2337/dc13-0695 [PMid:23949559]

[23] But A, De Bruin ML, Bazelier MT et al. Cancer risk among insulin users: comparing analogues with human insulin in the CARING five-country cohort study. Diabetologia. 2017; 60 (9): 1691-1703. DOI: https://doi.org/10.1007/s00125-017-4312-5 [PMid:28573394 PMCid:PMC5552833]