The results of several recent studies have indicated that some types of cancer are more common in diabetes (especially type 2 diabetes). This association was first reported as an incidental finding in 1932. It has been observed that diabetics have a higher risk of malignancy, especially cancer of the pancreas, liver, endometrium, breast, colon, rectum, and urinary bladder. However, the incidence of other types of cancer (e.g., lung, kidney, non-Hodgkin lymphomas) do not seem to be strongly associated with diabetes or the evidence is inconclusive. Interestingly enough, diabetes is associated with a lower risk for prostate cancer. Furthermore, clinical observations indicate that the prevalence of diabetes in newly diagnosed cancer patients ranges from 8% to 18%, suggesting bidirectional association between these two life-threatening diseases.

A number of studies have shown that cancer patients with preexisting diabetes have an increased risk of all-cause long-term mortality and of short-term mortality, especially in the peri- and postoperative period. However, the exact mortality rate attributable to cancer in diabetics remains unknown and it is possible that higher mortality risk associated with chronic hyperglycemia is independent of cancer.

Type 2 diabetes and cancer share several common potential risk factors (e.g., aging, sex, obesity, physical activity, diet, alcohol, and smoking). In type 2 diabetes, insulin resistance and hyperinsulinemia (either endogenous due to insulin resistance or induced by administration of exogenous insulin formulations) are considered to be independent risk factors for cancer development. In addition, hyperglycemia-related oxidative stress, accumulation of advanced glycation end products on proteins and other macromolecules as well as chronic low-grade inflammation may also enhance the risk of malignant transformation. Because recent publications have also suggested the link between hypoglycemic medications and cancer, the aim of our paper is to address this important clinical issue.
at sufficiently high supraphysiologic doses. Although several possible explanations for this association have been proposed, the mechanisms responsible for the development of cancer in patients with diabetes are not fully understood. It has long been suggested that compensatory hyperinsulinemia in the presence of insulin resistance may promote abnormal cell proliferation and growth. Evidence has accumulated showing that insulin has the ability to bind and activate not only the insulin receptor (IR) but also the insulin-like growth factor-1 receptor (IGF-1R). It is believed that metabolic action of insulin is associated with IR, while the mitogenic action correlates better with IGF-1R. Furthermore, numerous studies have demonstrated that IGF-1R is involved in carcinogenesis and cancer progression. Activation of IGF-1R by insulin evokes a series of reactions that may activate the mitogen-activated protein kinase (MAPK) signaling pathway and the phosphoinositol-3-kinase (PI3K) pathway. The PI3K pathway is responsible for metabolic effect of insulin because this pathway mediates insulin-stimulated translocation of the glucose transporter 4, while the MAPK signaling pathway plays a key role in the promotion of cell growth and proliferation. It has been demonstrated that under physiological conditions the MAPK pathway is inhibited and activated in the presence of insulin resistance. In addition, it has been reported that hyperinsulinemia suppresses hepatic production of IGF-1-binding protein and in turn increases the level of free fraction of IGF-1. It is well known that IGF-1 has even more potent mitogenic and antiapoptotic properties than insulin. It has been shown that various cancer cells have higher content of IR and IGF-1R on their surface than normal cells. Cancer cells predominantly express and activate the A isoform of IR, which has more potent mitogenic activity. Thus, the activation of IR may stimulate cancer cell proliferation. Moreover, hyperinsulinemia increases glucose uptake by highly insulin-sensitive tumor cells, which in turn supports tumor growth.

Recent studies have suggested that modifications of the amino acid sequence of human insulin may increase mitogenic properties of insulin analogs. Sandow emphasized that even single amino acid substitutions in insulin sequence may change the affinity for IR and IGF-1R. Structural similarities of IGF-1 and insulin glargine, a long-acting insulin analog that has modified B-chain (B31B32diArg) in the C-terminal region, have been recognized. Kurtzhals et al. using Chinese hamster ovary cells and osteosarcoma cells, have found a 6- to 8-fold increased IGF-1R affinity and mitogenic potency of insulin glargine compared with human insulin. On the other hand, insulin detemir, another long-acting insulin analog that has modified A-chain (A10A11Arg) in the N-terminal region, has been shown to have attachment of fatty acid chain to LysB29, revealed depletion in receptor affinities. Therefore, this analog does not significantly change the balance between mitogenic and metabolic properties. It may at least partially explain the lack of any clinical reports suggesting the association of this long-acting analog with cancer. However, it has recently been found that both insulin detemir and insulin glargine were able to activate IR and IGF-1R in the colon cancer lines HCT116. Insulin glargine was able to phosphorylate IGF-1R at 5-fold lower doses than those required to activate IR, and insulin detemir was significantly less potent in IGF-1R activation than insulin glargine. It has also been shown that insulin glargine can lead to prolonged activation of the receptors and therefore promote abnormal intracellular signaling.

Several studies have been performed to estimate the risk of malignant tumor development in patients with diabetes treated with human insulin and/or insulin analogs. However, the results raised considerable controversy. A number of clinical observations have shown a positive correlation between any type of insulin and specific types of cancer in diabetics. Recently, inhaled insulin has been withdrawn from the market by the manufacturer due to low popularity and high cost of the drug. However, this form of insulin was also linked with an increased risk of lung cancer, particularly in patients who had a prior history of cigarette smoking. Concern has also been raised that glargine may possibly increase the risk of malignancy, particularly breast cancer, in a dosedependent manner. On the other hand, it has been found that human insulin and short-acting insulin analogs do not affect cancer occurrence. Interestingly, Yang et al. reported that insulin use is associated with reduced cancer risk in Asian patients.

A population-based study in Sweden demonstrated that women using glargine monotherapy had a statistically higher risk of breast cancer compared with women using other types of insulin. Paradoxically, use of glargine in combination with other types of insulin did not increase cancer risk. Therefore, no definitive conclusion as to the association between glargine and malignancy may be drawn from this study. Also, the Scottish Diabetes Research Network Epidemiology Group did not observe an increased risk of total or site-specific cancer (breast) associated with overall glargine use. However, users of glargine alone had a significantly higher cancer incidence compared with users of other insulin types without glargine. Surprisingly, users of insulin glargine with other insulin formulations had a lower malignancy rate than diabetics treated with glargine monotherapy. Rosenstock et al. in a randomized controlled trial, did not observe increased cancer risk in the insulin glargine group compared with the neutral protamine Hagedorn insulin group. In the United Kingdom general practice setting, Currie et al. did not confirm the association between solid tumors, including breast cancer, and...
the use of insulin glargine or the premixed analogs. In addition, they found that patients on any type of insulin or insulin secretagogues were more likely to develop solid cancers than those on metformin or a combination of metformin with other antidiabetic agents. A meta-analysis of 31 randomized clinical trials including 10,880 diabetics showed no association of glargine with an increased incidence of cancer, including breast cancer, when compared with the control group. Similarly, a meta-analysis of clinical trials with insulin detemir conducted by Dejgaard et al. revealed no increase in cancer incidence in patients using this formulation. Finally, the Food and Drug Administration (FDA) has recently reported that an interim review of the data from the ongoing ORIGIN trial (Outcome Reduction With Initial Glargine Intervention) by an independent data monitoring committee did not show evidence that insulin glargine increased the risk of cancer. The FDA will continue to update the public as further information becomes available. For now, health care professionals should continue to follow the recommendations on the label when prescribing this drug and patients should maintain using it as directed unless told otherwise by their physician.

**Metformin** Numerous epidemiological observational and case-control studies, but not all, have shown that metformin monotherapy, in comparison with other hypoglycemic regimens, was associated with a reduced risk of cancer development and of mortality in patients with type 2 diabetes. Of note, adding metformin to insulin therapy also reduced progression to cancer. The ability of metformin to reduce cancer risk is likely to be independent of glucose-lowering effect and might be related to its indirect effects, such as compensatory insulin level reduction. Furthermore, accumulating evidence suggests that the potential role of metformin as an antitumor agent may be associated with its direct activation of 5' adenosine monophosphate-activated protein kinase (AMPK). This interaction may result in protein synthesis inhibition and significant repression of cell proliferation. Preclinical studies showed that metformin activating the AMPK pathway can indirectly inhibit the mammalian target of rapamycin, a downstream effector of growth factor signaling, and in turn prevent tumor cell proliferation.

Studies on mice revealed significant reduction of both breast epithelial cell proliferation and protein synthesis. These observations have been confirmed by Bodmer et al. who revealed the relationship between long-term metformin-based therapy and decreased risk of breast cancer in type 2 diabetes women. Of note, it was suggested that early-stage breast cancer in diabetic patients treated with metformin and neoadjuvant chemotherapy had better outcomes as measured by the pathologic complete response rate. Metformin in the management of breast cancer also proved to target the epithelial-mesenchymal transition, which is particularly important because through this molecular process, transformed epithelial cells can acquire the mesenchymal traits that provoke metastatic lesions. Hirsch et al. observed that metformin may selectively kill cancer stem cells and thus, acting synergistically with chemotherapeutics, improve the effectiveness of breast cancer treatment.

Libby et al. found that new users of metformin had a significantly lower risk of cancer than comparators. The observation of 1300 type 2 diabetes patients with no malignancies in history, who started insulin therapy between 1998 and 2007, showed that metformin use by insulin-treated patients was associated with significantly lower incidence of cancer in comparison with those who were using sulfonylureas. A meta-analysis of epidemiologic studies performed by DeCensi et al. revealed a 31% reduction in overall relative risk of some types of cancer incidence and cancer-related death in type 2 diabetes patients taking metformin compared with other antidiabetic drugs. ZODIAC (Zwolle Outpatient Diabetes Project Integrating Available Care) conducted in the Netherlands has been the first observational prospective study that showed lower cancer-related mortality in diabetics treated with metformin in a dose-dependent manner. The promising results of preclinical and observational studies support further investigations on metformin in cancer treatment and prevention. The efficacy of metformin on both recurrence and survival in early-stage breast cancer is currently being studied in phase III randomized clinical trials.

**Insulin secretagogues** There are two classes of insulin secretagogues: sulphonylureas, which are still among the most frequently used oral hypoglycemic medications to treat hyperglycemia in type 2 diabetes, and glinides. The main effect of their interaction with specific β-cell receptors results in insulin release from the intracellular stores. It has long been known that sulfonylurea-related hyperinsulinemia increases the risk of hypoglycemia and weight gain. Recently, several studies have suggested that these antidiabetic drugs may also increase the risk of cancer. Moreover, it has been reported that type 2 diabetics receiving sulfonylureas or exogenous insulin formulations have a significantly increased risk of cancer-related mortality compared with patients treated with metformin. In a population-based cohort study, Bowker et al. found that cancer-related mortality among residents of the province of Saskatchewan in Canada was greater for diabetics treated with insulin and sulphonylureas than for metformin users. The clinical trials investigating the relationship between sulphonylurea use and cancer occurrence have yielded inconsistent results. Several factors must be considered when analyzing the findings from observational studies that examine the association between diabetes
Thiazolidinediones  Thiazolidinediones (TZDs) are insulin-sensitizing agonists of the intracellular peroxisome-activated receptor γ. Therefore, if insulin resistance plays a crucial role in the association between increased cancer risk and type 2 diabetes, one may expect that TZDs exert an anticancer effect. This assumption has been confirmed in several preclinical studies. For example, it has been demonstrated that troglitazone inhibited the growth of human cancer cell lines in the lung, colon (HTC-116), breast (MCF-7), and prostate (PC-3) in immunodeficient mice. However, the results of clinical studies are controversial and burdened with weaknesses, such as a relatively recent TZD introduction to type 2 diabetes therapy, a small number of patients, a short follow-up period. Home et al., analyzing the results of ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials, have found lower occurrence of malignancies in type 2 diabetes patients treated with rosiglitazone and metformin compared with those treated with glibenclamide. Interestingly, they did not find any significant differences between tumor preventing effect of metformin and rosiglitazone. Of note, the European Medicines Agency recommended withdrawal of rosiglitazone from clinical use in 2010, mostly due to emerging concerns over excess cardiovascular risk including heart attack and heart failure. Nevertheless, rosiglitazone is still available in the United States with an FDA restriction that this drug should be prescribed with caution only to patients who cannot reach their treatment targets with other regimens. Govindarajan et al. conducted a retrospective analysis assessing the impact of TZD treatment on cancer incidence in diabetes patients. They have documented a 33% reduction in lung cancer risk in TZD users. Koro et al. did not observe any association between TZD treatment and the risk of breast, colon, and prostate cancer in TZD users compared with users of other antidiabetic medications. In contrast, Ramos-Nino et al. revealed that TZDs may increase the risk of cancer. All these controversial observations indicate that definite conclusions regarding cancer incidence in TZD-treated diabetics remain to be reached.

Incretin-based therapy  In the case of glucagon-like peptide-1 (GLP-1)-based drug therapy, including GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, preliminary evidence that suggests the potential risks of acute pancreatitis is perhaps of greatest concern. However, it must be underlined that the risk of pancreatitis and pancreatic cancer is higher in people with diabetes and obesity than in the healthy population. Experimental data also suggest that exenatide, liraglutide, and DPP-4 inhibitors increase β-cell proliferation and the risk of certain types of cancer in animals receiving these medications. It has been found that GLP-1 receptor (GLP-1R) activation stimulates calcitonin secretion and promotes the development of C-cell hyperplasia and medullary thyroid cancer (MTC) in rodents but not in monkeys, likely due to sustained GLP-1R activation. In humans, only slight increases in serum calcitonin were noted. Matveyenko et al. demonstrated that administration of DPP-4 inhibitor, sitagliptin, to the amyloid polypeptide (HIP) transgenic diabetic rats stimulated pancreatic duct cell replication and metaplasia and accompanying fibrosis in several animals. In addition, they noted extensive pancreatic ductal proliferation and metaplasia and accompanying fibrosis in three HIP rats treated with sitagliptin. Moreover, sitagliptin therapy induced acinar to ductal metaplasia in approximately 30% of treated animals. Acinar to ductal metaplasia follows increased ductal replication in the morphological progression of chronic pancreatitis to pancreatic adenocarcinoma. Preclinical tests have shown that liraglutide increases the risk of MTC in rats and mice. However, Knudsen et al. observed that after administration of liraglutide to monkeys for almost 2 years, there was no evidence either for increased calcitonin level or C-cell hyperplasia. Currently available data do not indicate any association between GLP-1R agonists and the incidence of any type of cancer in humans. Nevertheless, the FDA underlines the need for careful monitoring of annual incidence of malignancies in human using GLP-1 analogs and DPP-4 inhibitors.

Conclusions  Recent epidemiological studies, although inconclusive, have raised concerns about the increased risk of malignancies in type 2 diabetes patients associated with the use of antidiabetic medications. Preclinical, epidemiological, and clinical evidence suggests that metformin appears to inhibit proliferation and growth of some tumor cells in vitro and reduces cancer risk in diabetics in the clinical setting. These observations...
raise the possibility for future use of metformin in the treatment of malignancies in humans. On the other hand, some publications have suggested a higher risk of cancer in patients receiving insulin and sulfonylureas. Yet, the majority of the available studies assessing the effect of antidiabetic medications on cancer development have significant limitations, mainly because they did not take confounding factors into account. Despite the growing number of studies suggesting an association between cancer and antidiabetic drugs, there is an agreement that the available evidence does not suggest any imminent significant change in clinical practice, specifically with regard to insulin glargine. Further prospective randomized clinical trials are needed to clarify the association between the use of hypoglycemic medications and cancer development.

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Czy mamy wystarczające dane na potwierdzenie związku między stosowaniem leków przeciwcukrzycowych a rozwojem raka?

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SŁOWA KLUCZOWE

cukrzyca, leki przeciwcukrzycowe, nowotwory

STRESZCZENIE

Cukrzyca, zwłaszcza typu 2, jest związana z większym ryzykiem wystąpienia niektórych nowotworów. Mechanizmy odpowiedzialne za zwiększone ryzyko rozwoju nowotworów u pacjentów z cukrzycą nie są w pełni wyjaśnione. Wskazuje się na istotną rolę insulinooporności, hiperinsulinemii, stresu oksydacyjnego, produktów zaawansowanej glikacji oraz przewlekłego zapalenia małego stopnia. Wyniki ostatnich badań epidemiologicznych sugerują ponadto związek między terapią lekami przeciwcukrzycowymi a występowaniem nowotworów. Dostępne dane pisemnictwa, chociaż nierozstrzygające, mogą sugerować większe ryzyko raka u chorych otrzymujących niektóre leki hipoglikemizujące (np. insulinę i pochodne sulfonylomocznika). Z drugiej strony stosowanie metforminy lub rozyglitazonu może hamować rozwój nowotworu, przede wszystkim w odniesieniu do raka piersi. Celem naszego artykułu jest przedstawienie obecnego stanu wiedzy dotyczącej tego ważnego problemu klinicznego.