

# Glycated hemoglobin, diabetes treatment and cancer risk in type 2 diabetes. A case-control study

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## Abstract

**Introduction:** Type 2 diabetes is associated with an increased risk of some types of cancer. Diabetes treatment may also modify cancer risk.

**Objective:** The aim of this retrospective, case-control study was to assess whether HbA<sub>1c</sub> level and use of anti-diabetic drugs are associated with cancer development in a diabetic population.

**Materials and methods:** The case group consisted of 53 patients who developed cancer after diagnosis of diabetes. They were compared with 53 diabetic subjects without cancer, strictly matched to a case group by age and gender. In both groups – apart from HbA<sub>1c</sub> and diabetes treatment – demographic data, smoking habits, comorbidities, BMI, diabetes duration, use of aspirin, antihypertensive and hypolipemic drugs were also analyzed.

**Results:** Patients with cancer had a significantly higher mean HbA<sub>1c</sub> value compared with the control group, 7.83±1.26% vs. 7.30±1.08%, respectively (p=0.022). The distribution of patients in four HbA<sub>1c</sub> categories (<7.0, 7.0-7.9, 8.0-8.9 and ≥9.0%) was significantly different between the two groups (p=0.031). The probability of cancer was higher among patients with HbA<sub>1c</sub> value ≥8.0 % OR 3.160 (95% CI 1.342-7.440), p=0.013, and lower among patients using metformin, OR 0.228 (95% CI 0.083-0.633), p=0.006. The number of insulin users, insulin dose, duration of insulin treatment, and use of other anti-diabetic drugs were not significantly different between the two groups. Also, no significant differences were found between the two groups regarding other variables.

**Conclusions:** The presented case-control study indicated an important role of metabolic control and confirmed the protective role of metformin in reducing cancer risk among patients with type 2 diabetes. Contrary to other studies, insulin use was not associated with a higher risk of cancer. Other anti-diabetic drugs appeared to have a neutral impact on cancer development.

## Key words

type 2 Diabetes, cancer, HbA<sub>1c</sub>, metformin, insulin, obesity

## INTRODUCTION

There is mounting evidence confirming association between diabetes, predominantly type 2, and several types of cancer. Type 2 diabetes is associated with an increased risk of colorectal, pancreatic, hepatocellular, endometrial, breast, bladder and kidney cancers, and with non-Hodgkin lymphoma [1, 2, 3, 4, 5, 6, 7, 8]. In cancer development, both genetic and environmental factors are involved [9]. Among potential biological mechanisms directly linking diabetes and cancer, obesity, insulin resistance with compensatory hyperinsulinaemia, inflammation and hyperglycaemia are pointed out [10, 11, 12, 13]. Hyperglycaemia may play an important role in cancer development by serving as an energy source for proliferating cells [14].

Glucose-lowering therapy may also have an impact on cancer risk in diabetic subjects. Observational studies suggest a protective role of metformin on cancer development and outcomes. On the other hand, exogenous insulin and some sulphonylurea drugs are associated with an elevated cancer risk [10, 11, 12]. Also, a relationship between exenatide and sitagliptin use and pancreatic or thyroid (exenatide only)

cancer have been reported [15]. More recently, increased risk of bladder cancer in patients treated with pioglitazone has also been described [16, 17]. However, other factors associated with cancer risk in the diabetic population are not yet fully recognized.

## OBJECTIVE

The principal aim of this single-center retrospective, case-control study was to evaluate whether HbA<sub>1c</sub> level and diabetes treatment are associated with cancer risk among diabetic patients treated in an outpatient clinic in a real-life setting. The secondary objective was to analyze whether other factors, such as place of residence, smoking habits, co-morbidity, BMI, diabetes duration, use of aspirin, antihypertensive and hypolipemic drugs reveal associations with cancer development in this population.

## MATERIALS AND METHODS

In the clinic's database, 59 patients who developed cancer after diagnosis of diabetes were identified. 6 subjects were excluded due to the lack of HbA<sub>1c</sub> value before, or at the time of cancer diagnosis. The remaining 53 patients (28 men and

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25 women) were compared with the control group consisting of 53 diabetic subjects without cancer, strictly matched to case group by age and gender. These patients were selected from the database in the case-control manner, with the 1:1 ratio. For each 'case' patient, a 'control' subject with the same gender, and with the nearest date of birth was chosen. All included patients were of Caucasian race. In both groups, metabolic control (mean HbA<sub>1c</sub> from the preceding up to 3 years before cancer diagnosis), diabetes duration, anti-diabetic medications, including insulin use, insulin dose and duration of insulin treatment, were analyzed. Several other variables, such as place of residence (rural or urban), smoking habits, co-morbidity (hypertension, hyperlipidaemia and cardiovascular disease), BMI, use of aspirin, antihypertensive and hypolipemic drugs were also included into the analysis. Hypertension was considered if blood pressure values were  $\geq 140$  mm Hg for systolic, and  $\geq 90$  mm Hg for diastolic blood pressure or if antihypertensive drugs were used. Hyperlipidaemia was recognized if LDL-cholesterol level was  $\geq 100$  mg/dl (2.6 mmol/l) and/or triglycerides concentration was  $\geq 150$  mg/dl (1.7 mmol/l), or hypolipemic drugs were used. Cardiovascular disease was confirmed if the patient had a history of major cardiovascular event: non-fatal myocardial infarction, hospitalization for acute coronary syndrome, non-fatal stroke, revascularization or amputation. In the 'case' group, data from the time preceding cancer diagnosis were used in the analysis. Similarly, data for the control group were assessed from the same time as for the case group, e.g. if the 'case' patient had cancer diagnosed in September 2009, the data for his/her comparator were taken from the same period.

Statistical analysis of the data was performed using SigmaPlot for Windows version 12.3 (Systat Software Inc., San Jose, CA, USA). The numerical data comparing the two groups of patients were analyzed using unpaired Student's t-test, after performing a Shapiro-Wilk normality test and constant variance test. In case of normality and/or constant variance test failure, the Mann-Whitney rank sum test was performed. The categorical data were compared using  $\chi^2$  test. To assess the impact of other variables, multiple linear regression or multiple logistic regression tests were performed, respectively. Numerical data are expressed as mean  $\pm$  SD. A p value  $< 0.05$  was considered statistically significant.

## RESULTS

Detailed characteristics of case and control groups, with the P value for differences between these groups are presented in the Table 1.

Patients with cancer had significantly higher mean HbA<sub>1c</sub> value in comparison with the control group,  $7.83 \pm 1.26\%$  vs.  $7.30 \pm 1.09\%$ , respectively ( $p=0.022$ ) (Fig. 1). Adjusted to BMI, diabetes duration, smoking and comorbidities, this difference still remained significant ( $p=0.032$ ). The distribution of patients in four HbA<sub>1c</sub> categories ( $<7.0$ ,  $7.0-7.9$ ,  $8.0-8.9$  and  $\geq 9.0$  %) was significantly different in the two groups (two-sided p value 0.031) (Fig. 2). Each 1-step increment in HbA<sub>1c</sub> category was associated with an increased risk of cancer, OR 1.612 (95% CI 1.098-2.367),  $p=0.015$  for trend. After adjustment for BMI, diabetes duration, smoking and comorbidities, this relationship was even more pronounced,

**Table 1.** Characteristics of case and control groups

Parameter	Case	Control	p value
<b>Gender (n):</b>	-	-	N/A
Male	28	28	-
Female	25	25	-
<b>Date of birth (n):</b>	-	-	NS
Before 1/Jan/1930	4	4	-
1/Jan/1930 - 31/Dec/1939	24	24	-
1/Jan/1940 - 31/Dec/1949	17	17	-
1/Jan/1950 - 31/Dec/1959	7	7	-
1/Jan/1960 - 31/Dec/1969	1	1	-
<b>Cancer site (n):</b>	-	N/A	N/A
Colon/rectum	13	-	-
Breast	8	-	-
Pancreas	5	-	-
Prostate	5	-	-
Stomach	4	-	-
Lungs	3	-	-
Kidney	3	-	-
Other	12	-	-
<b>Place of residence (n):</b>	-	-	NS
Town >50,000 inhabitants	36	33	-
Town <50,000 inhabitants	3	7	-
Rural area	14	13	-
<b>Smoking habits (n):</b>	-	-	NS
Never smoker	28	24	-
Ex smoker	18	23	-
Current smoker	7	6	-
<b>Comorbidities (n):</b>	-	-	-
Hypertension	50	50	NS
Hyperlipidemia	48	41	NS (0.112)
Cardiovascular disease*	15	14	NS
<b>BMI (kg/m<sup>2</sup>) (n):</b>	-	-	NS
<25.0	7	6	-
25.0-29.9	17	16	-
$\geq 30.0$	29	31	-
Mean ( $\pm$ SD)	30.7 $\pm$ 5.5	30.6 $\pm$ 4.9	NS
<b>Diabetes duration (years)</b>	12.4 $\pm$ 8.7	10.8 $\pm$ 8.5	NS
<b>Diabetes treatment (n):</b>	-	-	-
Insulin	28	24	NS
<50 IU/day	16	16	NS
$\geq 50$ IU/day	12	8	NS
no insulin	25	29	NS
insulin duration (years) (mean $\pm$ SD)	7.7 $\pm$ 6.8	6.1 $\pm$ 5.2	NS
Metformin	34	47	0.006
Sulfonylurea	27	29	NS
Acarbose	12	4	NS (0.058)
Incretins	2	0	NS
<b>HbA<sub>1c</sub> (%) (n)</b>	-	-	0.031
<7.0	17	22	-
7.0-7.9	12	20	-
8.0-8.9	12	8	-
$\geq 9.0$	12	3	-
Mean ( $\pm$ SD)	7.83 $\pm$ 1.26	7.30 $\pm$ 1.08	0.022
Aspirin	36	38	NS
Statins	36	32	NS
Fibrates	9	8	NS
ACE-I/ARB	44	43	NS
Calcium antagonists	21	21	NS
Diuretics	31	34	NS
Beta-blockers	39	37	NS
Alpha-blockers	5	6	NS

N/A – non applicable; NS – non-significant

\* non fatal myocardial infarction, hospitalized acute coronary syndrome, non fatal stroke, revascularization, amputation

OR 1.676 (95% CI 1.106-2.538)  $p=0.015$ . In comparison with patients with good metabolic control of diabetes (HbA<sub>1c</sub>  $< 7.0\%$ ), every 0.5% increment of HbA<sub>1c</sub> value was associated with an increasing cancer risk, with the cut-off

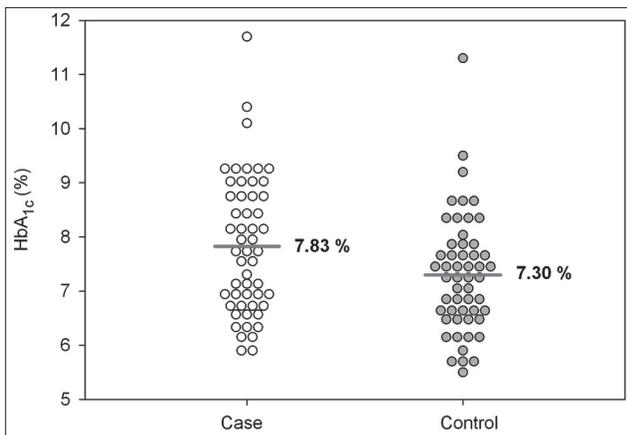


Figure 1. Histogram plot of HbA<sub>1c</sub> distribution in case and control groups

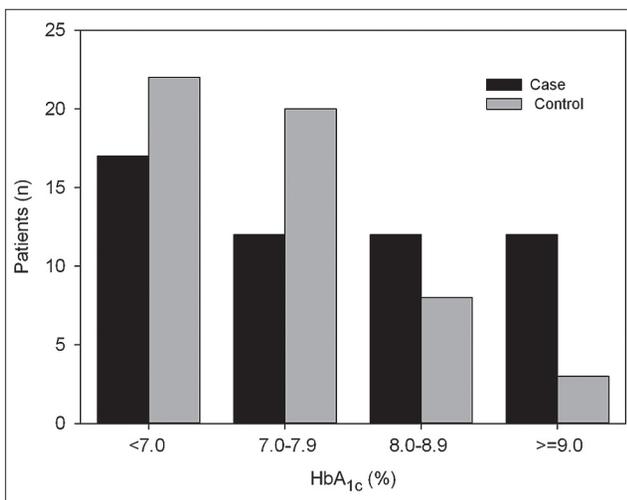


Figure 2. Distribution of patients in the four HbA<sub>1c</sub> categories

point at the HbA<sub>1c</sub> level  $\geq 8.0\%$  (Fig. 3). Patients with HbA<sub>1c</sub> value  $\geq 8.0\%$ , compared with those with HbA<sub>1c</sub>  $< 8.0\%$ , had a significantly higher probability of cancer development, OR 3.160 (95% CI 1.342-7.440),  $p=0.013$ . After adjustment for diabetes duration, BMI, smoking and comorbidities, cancer risk in this group was even higher, OR 3.594 (95% CI 1.450-8.910),  $p=0.006$ .

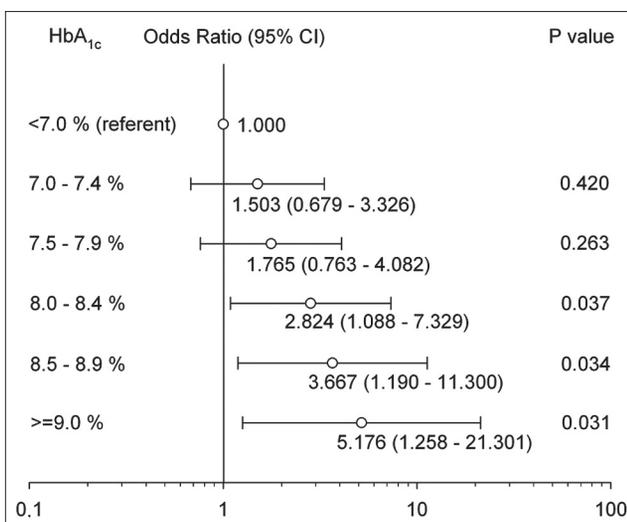


Figure 3. Cancer probability according to mean HbA<sub>1c</sub> level (HbA<sub>1c</sub>  $< 7.0\%$  - referent)

Among patients with cancer, the number of metformin users ( $n=34$ ) was significantly lower compared with the control group ( $n=47$ ). The probability of cancer development among patients using metformin was significantly lower compared with non-users, OR 0.228 (95% CI 0.083-0.633),  $p=0.006$ . After adjustment for insulin and other anti-diabetic drugs use, the difference still remained significant, OR 0.262 (95% CI 0.090-0.768),  $p=0.015$ .

The number of insulin users and also the number of patients with insulin dose  $< 50$  IU or  $\geq 50$  IU were not significantly different between the two groups. A trend towards longer duration of insulin treatment in the case group was observed, but this was not statistically significant ( $p=0.456$ ).

Other anti-diabetic drugs appeared to have a neutral impact on cancer probability, with the exception of acarbose. In the univariate analysis, a borderline association between acarbose use and risk of cancer was noted, OR 3.585 (95% CI 1.074-11.966),  $p=0.058$ . However, after adjustment for insulin and other anti-diabetic drugs use, this relationship was attenuated, OR 2.537 (95% CI 0.703-9.152),  $p=0.155$ .

In the univariate analysis, no significant differences between the two groups regarding place of residence, smoking habits and comorbidities were found. In both groups the number of patients with three BMI categories (normal, overweight and obesity) was similar. Mean BMI was almost identical in the case and control groups. Use of aspirin, hypolipemic and anti-hypertensive drugs were not significantly different between the two groups.

## DISCUSSION

In this single-center, retrospective, case-control study, patients treated in the diabetes outpatient clinic in a real-life setting were included. In this population significant, a correlation between long-term metabolic control of diabetes and cancer risk was revealed. Mean HbA<sub>1c</sub> value was significantly higher in a cancer group relative to the control group. Subjects with higher HbA<sub>1c</sub> values also appeared to have an increased probability of cancer development in comparison with better controlled patients with diabetes. Rapid elevation of this risk was observed among patients with HbA<sub>1c</sub> level  $\geq 8.0\%$ . This relationship was independent of BMI and diabetes duration (due to the study design, the patients were strictly matched regarding age and gender). Also, treatment of diabetes appeared to have an impact on cancer risk. Metformin use was associated with significantly lower probability of cancer development. Other anti-diabetic drugs, including insulin, did not show any relationship with cancer risk.

Associations between hyperglycaemia and cancer development have been evaluated since the early 1970s. Heuson et al. in their experimental study demonstrated accelerated growth of breast cancer in rats after infusion of 10% glucose solution [18]. A relationship between the level of fasting plasma glucose (FPG) and cancer in human studies in the European populations has been documented in several papers. In all these studies, both non-diabetic and diabetic subjects were included. A risk of combined cancers in a population of 63,585 men and 77,228 women in Austria, followed for 8.4 years, was associated with FPG in a diabetic range ( $\geq 7.0$  mmol/l) relative to the FPG level 4.2–5.2 mmol/l (HR 1.20; 95% CI 1.03-1.39 in men and

1.28; 95% CI, 1.08–1.53 in women) [19]. In a prospective study of a large cohort of 33,293 women and 31,304 men in Sweden, 2,478 new cases of cancer were identified. Total cancer risk was elevated for the top versus bottom quartile of FPG in women, and in women and men combined, while was not observed in men. In this study, cancer risk increment appeared to be independent of obesity [20]. In the Metabolic syndrome and Cancer project (Me-Can) cohorts of 274,126 men and 275,818 women from Norway, Austria, and Sweden were included. During the 10.4 years of prospective observation, 18,621 men and 11,664 women developed cancer. Each 1 mmol/l increment of FPG was associated with the significant increase in cancer incidence in men, RR 1.05 (95% CI 1.01-1.10), and in women, RR 1.11 (95% CI 1.05-1.16) [21]. In a case-control study in northern Sweden, the relationship between metabolic syndrome components and colorectal cancer risk were examined. Neither BMI, nor blood pressure, systolic (SBP) or diastolic (DPB), fasting or post-load plasma glucose alone showed a significant correlation with cancer risk. Regarding long-term metabolic control, subjects in the highest versus the lowest decile of HbA<sub>1c</sub> had borderline elevated risk of colorectal cancer, OR 1.83 (95% CI 1.00-3.36;  $p=0.051$ ) [22].

Data regarding the relationship between cancer risk and HbA<sub>1c</sub> are divergent. In the European Prospective Investigation into Cancer-Norfolk Study, HbA<sub>1c</sub> value appeared to correlate with a risk of colorectal cancer among both women and men. Every 1% absolute increase in HbA<sub>1c</sub> level was associated with a 34% increment of cancer risk ( $p<0.001$ ). Known diabetes was associated with a 3-fold higher risk of incident cancer. Also, in the diabetic group every 1% increment of HbA<sub>1c</sub> level was associated with elevated cancer risk, adjusted RR 1.30 (95% CI 1.04-1.61),  $p=0.02$  [23]. In a case-control study assessing colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort, 1,026 (561 men and 465 women) incident cancer cases were found. In comparison with the 1,026 matched control subjects, a 10% increment of HbA<sub>1c</sub> was associated with a mild increase of cancer risk, OR 1.10 (95% CI 1.01-1.19) [24]. In a population of 12,792 men and women free of cancer at baseline, taken from the Atherosclerosis in Communities (ARIC) Study, 2,349 new cancer cases and 887 cancer deaths during 14-16 years of observation were noted. Compared with non-diabetic women with lower (5.0-5.6%) HbA<sub>1c</sub> level, non-diabetic women, with higher HbA<sub>1c</sub> values ( $\geq 5.7\%$ ), and diabetic women, presented a higher risk of cancer incidence: HR 1.24 (95% CI 1.07-1.44) and 1.30 (95% CI 1.06-1.60), respectively, and also higher cancer mortality, HR 1.58 (95% CI 1.23-2.05) and 1.96 (95% CI 1.40-2.76), respectively. Diabetic women with good glycaemic control had a lower cancer risk relative to those with higher values. Such associations were not observed among men [25]. In the retrospective study by Donadon et al., patients with hepatocellular cancer ( $n=145$ ) had higher HbA<sub>1c</sub> values in comparison with diabetic subjects without cancer ( $n=62$ ),  $7.5\pm 1.8\%$  vs.  $6.8\pm 1.5\%$  respectively ( $p=0.0001$ ). Also metformin use was associated with lower cancer probability, OR 0.149 (95% CI 0.039-0.507),  $p=0.0054$  [26]. However, a relationship between cancer risk and HbA<sub>1c</sub> level was not found in all studies. In a case-control study by Yang et al., 2 groups of patients who had undergone colonoscopy (analysis 1) or sigmoidoscopy (analysis 2) were included. In the first group, among 4,248 patients, 1,296 (31%) of them

had at least 1 colorectal adenoma. Mean HbA<sub>1c</sub> level among patients without any adenomas was 8.20% compared with 8.26% in the group with at least 1 adenoma. This difference was not statistically significant ( $p=0.16$ ). In the second group consisting of 9,813 patients, 951 subjects (10%) had at least 1 distal adenoma. HbA<sub>1c</sub> level in patients without adenoma was 8.32% versus 8.37% in subjects with at least 1 adenoma. Also, this difference did not reach statistical significance ( $p=0.25$ ) [27]. In a prospective study, the predictive value of HbA<sub>1c</sub> concentration for breast cancer incidence was evaluated in 27,110 female participants of the Women's Health Study, free of cancer at baseline. During observation lasting 10 years, 790 cases of invasive breast cancer were confirmed. The highest quintile relative to the lowest quintile of baseline HbA<sub>1c</sub> value was not associated with an elevated risk of cancer, adjusted RR was 0.87 (95% CI, 0.69-1.10),  $p_{\text{trend}} = 0.22$  [28].

In the presented study, the mean HbA<sub>1c</sub> level in patients with cancer was significantly higher compared with the control group. In the papers discussed above, only the studies by Donadon et al. and Young et al. were performed solely in a diabetic population [26, 27]. All other studies were conducted in both non-diabetic and diabetic subjects. This could be an important difference. The deleterious effect of glucose, although it may also be seen in a higher versus lower values within a normal range, it can be more pronounced in high glucose concentrations. Prolonged exposure to hyperglycaemia induces formation of the reactive oxygen species (ROS) and leads to accumulation of advanced glycation end products (AGEs). The binding between AGEs and their receptor (RAGE) induces several biological effects. One of them is increased inflammation through the activation of the nuclear transcription factor NF- $\kappa$ B and formation of ROS in the cells, which may induce damage of nuclear DNA. Activation of this pathway is considered to play an important role, not only in inflammation, but also in carcinogenesis [29,30]. In the presented study, only subjects with diabetes were included, both in the case and in the control groups. Prolonged hyperglycaemia and/or glucose excursions observed in this population may activate these biological processes. Thus, a higher HbA<sub>1c</sub> value, which reflects long-term exposure to high glucose concentration, may be responsible, at least in part, for an increased risk of cancer in poorly controlled diabetic patients, which has also been demonstrated by Donadon et al. in their study on hepatocellular cancer [26].

Due to its progressive nature, type 2 diabetes requires intensification of treatment over time, beginning from monotherapy, through 2-3 oral drugs up to insulin treatment in different regimens. Thus, a clear impact of antidiabetic medications on cancer risk among diabetic patients is not easy to determine. Nevertheless, in many observational studies reduced risk of cancer was observed among patients using metformin. Metformin, according to many clinical practice recommendations, is considered a first-line therapy in type 2 diabetes [31, 32, 33]. The beneficial effect of this drug on cancer risk may be due to its direct and/or indirect impact on insulin resistance and circulating insulin level, as well as on the AMP-activated protein kinase (AMPK) signalling pathway. Metformin also inhibit the first step of mammalian target of rapamycin (mTOR) pathway, which is known to play a role in cell growth and proliferation. These observations have been thoroughly discussed in several

review papers [11, 12, 34, 35]. Other anti-diabetic drugs do not demonstrate such benefits. Inversely, several observational and epidemiological studies indicate the association between insulin treatment and increased cancer risk [10, 11, 12, 13]. Recently published systematic reviews and meta-analysis of case-control and cohort studies with 562,043 participants and 14,085 cases of cancer, confirmed this relationship, showing increased overall cancer risk among insulin-treated patients, RR 1.39 (95% CI 1.14-1.70) [36]. An elevated risk of cancer was also found for some sulfonylurea drugs [10, 11, 12, 13]. In recent months, some concerns regarding the oncological safety of thiazolidinediones and incretin drugs have been arisen [15, 16, 17]. An increased risk of breast and bladder cancer among patients using SGLT-2 inhibitors has also been pointed out [37].

In the presented study, the preventive effect of metformin on cancer risk was also found. This effect was independent of other anti-diabetic drugs use. Contrary to other observations, insulin use was not associated with increased cancer risk. Neither insulin dose nor duration of insulin treatment showed a significant impact on cancer development among patients included in the study. A possible explanation of this finding may be better metabolic control achieved with insulin treatment, which may counterbalance mitogenic effects of this hormone. Also, the number of patients using higher doses of insulin ( $\geq 50$  IU a day) was not large. Other anti-diabetic drugs also did not reveal any association with cancer risk. The borderline relationship found for acarbose may be explained by its use instead of metformin among patients intolerant to this drug.

Obesity is associated with several types of cancer, among both men and women [38]. However, such a relationship was not found in the presented study. Mean BMI was very similar in the case and in the control groups. Also, the distribution of patients in the 3 categories of BMI was not significantly different between the groups. In the presented study, other factors, such as rural or urban place of residence, smoking habits, comorbidities or use of aspirin, antihypertensive and hypolipemic drugs, did not appear to be associated with cancer risk. The study also has some limitations, the most important being the relatively small group of patients. This is associated with the smaller statistical power of the presented findings. Thus, a possible random effect cannot be totally excluded. On the other hand, some non-significant trends observed in this study would reach statistical significance in a larger group of patients. The second limitation is the single-centre design which did not allow the analysis of patients from different populations, treated by different health-care providers, and using different treatment regimens. Larger, multi-centre studies could be a solution to these limitations.

## CONCLUSION

The presented study indicates an important role of hyperglycaemia in cancer development in type 2 diabetic patients. The cancer probability considerably increases above the HbA<sub>1c</sub> threshold of 8.0%. Thus, efforts to achieve good metabolic control of diabetes are of value, not only in the context of the reduction of the risk of micro- and macrovascular complications, but also in the reduction of cancer risk in diabetic subjects.

Metformin, if not contraindicated or intolerant, should be used from the beginning through all stages of type 2 diabetes treatment, not only for its cardiovascular benefits, but also due to its protective role in cancer development.

Insulin use appeared to be harmless in terms of oncological safety. Other anti-diabetic drugs also did not show any association with elevated cancer risk.

Larger, multi-centre studies are necessary to confirm or exclude the findings revealed in this retrospective, case-control study.

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