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ORIGINAL REPORT

Insulin and other antidiabetic drugs and hepatocellular carcinoma risk: a nested case-control study based on Italian healthcare utilization databases

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ABSTRACT

Purpose Insulin and other antidiabetic drugs may modulate hepatocellular carcinoma (HCC) risk in diabetics.
Methods We have analyzed the role of various antidiabetic drugs on HCC in a nested case-control study using the healthcare utilization databases of the Lombardy Region in Italy. This included 190 diabetic subjects with a hospital discharge reporting a diagnosis of malignant HCC and 3772 diabetic control subjects matched to each case on sex, age, date at cohort entry, and duration of follow-up.
Results Increased risks of HCC were found for use of insulin (odds ratio [OR] = 3.73, 95% confidence interval [CI] 2.52–5.51), sulfonylureas (OR = 1.39, 95%CI 0.98–1.99), and repaglinide (OR = 2.12, 95%CI 1.38–3.26), while a reduced risk was found for use of metformin (OR = 0.57, 95%CI 0.41–0.79). The risk of HCC increased with increasing duration of insulin use (OR = 2.52 for <1 year, 5.41 for 1–2 years, and 6.01 for ≥2 years; p for trend < 0.001), while no clear pattern with duration was observed for sulfonylureas, repaglinide, and metformin.
Conclusion Our study supports the evidence that patients with diabetes using metformin, and possibly other antidiabetic drugs that increase insulin sensibility, have a reduced risk of HCC, while those using insulin or drugs that increase circulating insulin, such as insulin secretagogues, have an increased risk. Whether these associations are causal, or influenced by different severity of diabetes and/or possible residual bias or misclassification, is still open to discussion. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—antidiabetics; diabetes; hepatocellular carcinoma; insulin; metformin; pharmacoepidemiology

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INTRODUCTION

Type 2 diabetes mellitus has been associated with an over two-fold excess risk of hepatocellular carcinoma (HCC).[1–4] Although the mechanisms responsible for such a relation are not clear, hyperinsulinemia, insulin resistance, and the consequent up-regulation of the insulin-like growth factor system appear to be a possible link between the two conditions.[5–7]

Insulin and other antidiabetic drugs that act by regulating insulin production or sensitivity may also modulate HCC risk in diabetics. Thus, metformin,[8–16] and possibly thiazolidinediones (TZD),[9,12,17–19] has been associated with a reduced risk of HCC, whereas sulfonylureas[8,9,14] and insulin[8,9,14,17,20] to an increased risk. In particular, a meta-analysis reported a significantly 50% reduced incidence of HCC in metformin users and reported a 62% and 161% increase in sulfonylureas and insulin users, respectively.[21] However, the evidence on the role of specific antidiabetics on HCC risk is still limited and inconsistent;[16,18,21,22] furthermore, most studies were conducted in Asian populations at high risk for HCC.

We have therefore analyzed the role of various antidiabetic drugs on HCC risk in a large population-based study from Italy. In Italy, the incidence of liver cancer

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is estimated around 11.0/100,000 men (age-standardized, world) and 3.6/100,000 women in 2012, and the prevalence of diabetes is around 4% in 2011.[23,24]

MATERIAL AND METHODS

Data source

The data used for the present study were retrieved from the healthcare utilization databases of Lombardy, an Italian region, which includes about 10 million inhabitants. The Italian population is covered by the National Health Service (NHS), and in Lombardy, an automated system of databases has been created since 1997 to collect a variety of information, including the following: (1) an archive of residents who receive NHS assistance (the whole resident population, updated to December 2012), reporting demographic and administrative data and including information on vital status and, in case, date of death; (2) a database on outpatient drug prescriptions reimbursable by the NHS, including antidiabetic drugs (2000–2012); (3) a database on diagnosis at discharge from public or private hospitals of the region (2000–2012); and (4) a database containing all the exemption codes per pathology. For each patient, we linked the aforementioned databases via a single identification code. In order to preserve privacy, each identification code was automatically converted into an anonymous code; the inverse process was prevented by deletion of the conversion table.[25]

Study population

From the regional outpatient drug prescription database, we selected all subjects with at least one antidiabetic drug prescription (Anatomical Therapeutic Chemical, ATC, codes starting with A10[26]) between 1 January 2005 and 31 December 2007. For each subject, the first prescription of an antidiabetic drug was defined as the data at cohort entry. In order to identify new antidiabetic users only, we excluded subjects with either a prescription of antidiabetic drug, or an exemption for diabetes (coded as 013.250 in the exemption database), or a hospital discharge reporting a diagnosis of diabetes (International Classification of Disease, Ninth Revision, ICD9, code 250) in the 2 years preceding the cohort entry. Moreover, we excluded subjects with the following: (i) <40 or >80 years of age at cohort entry (to exclude most patients with type 1 diabetes mellitus and subjects with a highly compromised health status); (ii) either a hospital discharge reporting a diagnosis of (any) cancer or an exemption for cancer in the 5 years preceding the cohort entry (to avoid misclassification of prevalent HCC cases as incident diagnoses); (iii) a diagnosis of cancer during the first year of follow-up (to consider a minimum latency period); and (iv) no refill of an antidiabetic drug during the first 6 months of follow-up (sporadic users). We followed all patients from the date at cohort entry to the earliest between diagnosis of any cancer, death from any cause, emigration, and end of the follow-up (31 December 2012).

Case-control selection

Within the selected cohort, we conducted a nested case-control study. HCC cases were subjects with a hospital discharge reporting a diagnosis of malignant HCC (ICD9 code 155.0) during the follow-up. To avoid the inclusion of non-primary liver cancers (i.e., local or distant recurrences), we considered only the first cancer diagnosis. We defined the date of diagnosis of HCC as the index date. For each HCC case, we randomly selected up to 20 controls from the case subject's risk set and matched on sex, age (±1 year), date at cohort entry (±14 days), and duration of follow-up. By definition, control subjects were alive and at risk of developing HCC at the index date of the corresponding case.

Exposure definition

For each case and control, we obtained information of antidiabetic prescriptions between the cohort entry and the index date. We classified antidiabetic drugs in the following classes: insulin and insulin analogs, metformin, sulfonylureas, and other antidiabetic drugs (including TZD, α-glucosidase inhibitors, incretins, and repaglinide). When possible, we also analyzed separately each drug in the other antidiabetic drug category. Subjects using antidiabetic drug combinations (fixed or extemporaneous) were reallocated into each separate antidiabetic drug categories. We defined ever exposure to each type of antidiabetic drug by having at least one prescription of the corresponding antidiabetic drug during the follow-up. We also estimated the cumulative duration of exposure to each antidiabetic drug by dividing the total quantity of drug reported on each prescription by the corresponding defined daily dose[26] and summing up the duration associated to each prescription during the follow-up.

Statistical analysis

We used conditional logistic regression models to estimate the risk of HCC for each drug exposure in terms of ORs and their corresponding 95%CIs, using the matching variables age, sex, date at cohort entry, and

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duration of follow-up.[27] Further analyses were conducted adjusting risk estimates for the Charlson's comorbidity index,[28] hospital admission for cardio/cerebrovascular diseases (in the 5 years before cohort entry), prescription of antihypertensive drugs, antiplatelet drugs, and statins (in the 5 years before cohort entry), and use of other antidiabetic drugs (during follow-up). In first analyses, based on an "intention-to-treat" approach, we evaluated the risk of HCC associated with the use of antidiabetic drug at cohort entry; in secondary analyses, based on an "as-treated" approach, we assessed the risk of HCC in relation with ever use of each antidiabetic drug during the follow-up. In the latter case, we also analyzed the relation with cumulative duration of use.

RESULTS

Among 474,459 subjects with prescriptions of an antidiabetic drug during 2005–2007, 50,331 met the criteria of inclusion in the cohort (Supplemental Fig. 1). Subjects were followed-up for a mean of 6.0 years (SD 1.4 years). One-hundred and ninety subjects with a diagnosis of HCC were identified among 304,064 person-years of follow-up, corresponding to an overall rate of HCC of 62.5 per 100,000 person-years.

Table 1 shows the baseline characteristics of the 190 HCC cases and 3772 corresponding controls. By design, cases and controls had the same distribution in terms of sex and age. Cases had a higher Charlson's comorbidity index and reported more frequently the use of antihypertensive drugs and less frequently the use of and antiplatelet drugs and statins; no difference was found with reference to hospitalization for cardio/cerebrovascular diseases. At cohort entry, 11% of cases were using insulin/insulin analogs, 24% metformin, 45% sulfonylureas, 5.3% other antidiabetic drugs, and 15% combinations of antidiabetic drugs; corresponding figures for controls were 2.2%, 40%, 40%, 2.3%, and 16%.

The ORs for HCC in relation with the use of various antidiabetic drugs at cohort entry are shown in Table 2. Insulin was directly associated with the risk of HCC (OR = 3.78, 95%CI 2.05–6.95), the excess risk being higher for insulin analogs (OR = 6.36, 95%CI 2.80–14.45) than for human/animal insulin (OR = 1.88, 95%CI 0.80–4.42). HCC risk was significantly reduced for metformin (OR = 0.67, 95%CI 0.48–0.95), while no significant associations were observed for sulfonylureas (OR = 1.26, 95%CI 0.89–1.77) and other antidiabetic drugs (OR = 1.47, 95%CI 0.68–3.17).

Similarly, when considering antidiabetic drug use during follow-up (Table 3), increased risks were found for insulin (OR = 3.73, 95%CI 2.52–5.51, in particular insulin analogs OR = 4.40, 95%CI 2.82–6.88) and sulfonylureas (OR = 1.39, 95%CI 0.98–1.99), while a reduced risk was found for metformin (OR = 0.57, 95%CI 0.41–0.79). Among other antidiabetics, the ORs were 0.52 (95%CI 0.24–1.12) for TZD, 2.98 (95%CI 0.94–9.42) for α-glucosidase inhibitors, 0.30 (95%CI 0.04–2.26) for incretins, and 2.12 (95%CI 1.38–3.26) for repaglinide.

The risk of HCC increased with increasing duration of insulin use (OR = 2.52 for <1 year, 5.41 for 1–2 years, and 6.01 for ≥2 years; p for trend < 0.001), while no

Table 1. Baseline characteristics of 190 hepatocellular carcinoma cases and 3772 controls

	Cases		Controls		
	N	%	*N*	%	*p*-value*
Sex					—
Men	143	75.2	2837	75.2	
Women	47	24.8	935	24.8	
Age (years)					—
<50	14	7.4	245	6.5	
50–59	32	16.8	646	17.1	
60–69	71	37.4	1435	38.0	
≥70	73	38.4	1446	38.3	
(mean ± SD)	65.2 (9.1)		65.3 (9.0)		
Cardio/cerebrovascular diseases†					
No	179	94.2	3422	90.7	0.103
Yes	11	5.8	350	9.3	
Charlson's comorbidity index†					<0.001
0	137	72.1	3327	88.2	
≥1	53	27.9	445	11.8	
(mean ± SD)	0.59 (1.34)		0.18 (0.58)		<0.001
Antihypertensive drugs‡					
No	49	25.8	1228	32.6	0.052
Yes	141	74.2	2544	67.4	
Antiplatelet drugs‡					
No	148	77.9	2684	71.2	0.045
Yes	42	22.1	1088	28.8	
Statins‡					
No	175	92.1	2716	72.0	<0.001
Yes	15	7.9	1056	28.0	
Antidiabetic drugs§					
Insulin/Insulin analogs	20	10.5	83	2.2	<0.001
Insulin¶	9	4.7	52	1.4	<0.001
Insulin analogs‖	10	5.3	27	0.7	<0.001
Combinations	1	0.5	4	0.1	0.111
Metformin	45	23.7	1499	39.7	<0.001
Sulfonylureas	86	45.3	1497	39.7	0.126
Other antidiabetics	10	5.3	86	2.3	0.009
Combinations	29	15.3	607	16.1	0.761

*p-value from χ^2-test for categorical variables and from t-test for continuous variables.
†Hospital admission in the 5 years before cohort entry.
‡Index prescription in the 5 years before cohort entry.
§Index prescription at cohort entry.
¶Including human and animal insulin.
‖Including lispro, aspart, glulisine, degludec, detemir, and glargine.
SD, standard deviation.

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Table 2. Odds ratio (OR) of hepatocellular carcinoma and corresponding 95% confidence interval (CI) in relation with the use of various antidiabetic drugs at cohort entry

Use of antidiabetic drug	Cases (%)	Controls (%)	OR* (95%CI)	OR* (95%CI)
Insulin/insulin analogs				
No	170 (89.5)	3683 (97.6)	1‡	1‡
Yes	20 (10.5)	89 (2.4)	4.76 (2.88–7.89)	3.78 (2.05–6.95)
Metformin				
No	116 (61.1)	1679 (44.5)	1‡	1‡
Yes	74 (38.9)	2093 (55.5)	0.51 (0.38–0.68)	0.67 (0.48–0.95)
Sulfonylureas				
No	75 (39.5)	1686 (44.7)	1‡	1‡
Yes	115 (60.5)	2086 (55.3)	1.25 (0.92–1.68)	1.26 (0.89–1.77)
Other drugs				
No	180 (94.7)	3657 (96.9)	1‡	1‡
Yes	10 (5.3)	115 (3.1)	1.77 (0.91–3.43)	1.47 (0.68–3.17)

*Estimates from conditional logistic regression models, conditioned on sex, age, date at cohort entry, and duration of follow-up.
†Estimates further adjusted for Charlson's comorbidity index, cardio/cerebrovascular diseases, use of antipertensive drugs, use of antiplateletes drugs, and use of statins in the 5 years before cohort entry.
‡Reference category.

Table 3. Odds ratio (OR) of hepatocellular carcinoma and corresponding 95% confidence interval (CI) in relation with the use of various antidiabetic drugs during follow-up

Use of antidiabetic drug	Cases (%)	Controls (%)	OR* (95%CI)	OR* (95%CI)
Insulin/insulin analogs				
Never	140 (73.7)	3524 (93.4)	1‡	1‡
Ever	50 (26.3)	248 (6.6)	5.23 (3.67–7.47)	3.73 (2.52–5.51)
Metformin				
Never	82 (43.2)	960 (25.5)	1‡	1‡
Ever	108 (56.8)	2812 (74.6)	0.43 (0.32–0.59)	0.57 (0.41–0.79)
Sulfonylureas				
Never	54 (28.4)	1320 (35.0)	1‡	1‡
Ever	136 (71.6)	2452 (65.0)	1.36 (0.98–1.89)	1.39 (0.98–1.99)
Thiazolidinediones				
Never	182 (95.8)	3494 (92.6)	1‡	1‡
Ever	8 (4.2)	278 (7.4)	0.54 (0.26–1.12)	0.52 (0.24–1.12)
α-glucosidase inhibitors				
Never	186 (97.9)	3746 (99.3)	1‡	1‡
Ever	4 (2.1)	26 (0.7)	3.13 (1.08–9.09)	2.98 (0.94–9.42)
Incretins				
Never	189 (99.5)	3762 (99.7)	1‡	1‡
Ever	1 (0.5)	10 (0.3)	0.20 (0.03–1.47)	0.30 (0.04–2.26)
Repaglinide				
Never	157 (82.6)	3475 (92.1)	1‡	1‡
Ever	33 (17.4)	297 (7.9)	2.46 (1.66–3.64)	2.12 (1.38–3.26)

*Estimates from conditional logistic regression models, conditioned on sex, age, date at cohort entry, and duration of follow-up.
†Estimates further adjusted for Charlson's comorbidity index, cardio/cerebrovascular diseases, use of antipertensive drugs, use of antiplateletes drugs, use of statins (in the 5 years before cohort entry), and for use of other antidiabetics (during follow-up).
‡Reference category.

clear pattern with duration of use was observed for metformin (ORs = 0.59, 0.61, and 0.52), sulfonylureas (ORs = 1.73, 1.08, and 1.44), and repaglinide (ORs = 2.30, 1.29, and 1.91, Table 4).

DISCUSSION

Our study, based on a uniquely large cohort of antidiabetic drug utilizers, indicates that use of metformin reduces the risk of HCC, while insulin and other antidiabetic drugs that stimulate insulin production (as sulfonylureas and repaglinide) are associated with an increased risk. A duration–risk relationship was observed for insulin. With reference to other antidiabetics, TZD are associated with a nonsignificant-reduced risk of HCC, whereas α-glucosidase inhibitors might increase the risk, although the numbers of users for these drugs were too limited to draw definite conclusions.

Our findings are consistent with the evidence from most previous investigations on the issue which

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Table 4. Odds ratio (OR) of hepatocellular carcinoma and corresponding 95% confidence interval (CI) in relation with the duration of use of various antidiabetic drugs during follow-up

Duration of antidiabetic drug use (years)	Cases (%)	Controls (%)	OR* (95%CI)	OR* (95%CI)
Insulin/insulin analogs				
No use	140 (73.7)	3524 (93.4)	1‡	1‡
<1	21 (11.0)	152 (4.0)	3.59 (2.20–5.86)	2.52 (1.49–4.26)
1–2	10 (5.3)	39 (1.0)	6.58 (3.23–13.38)	5.41 (2.44–12.00)
≥2	19 (10.0)	57 (1.5)	8.92 (5.08–15.66)	6.01 (3.10–11.64)
p-value for trend			<0.001	<0.001
Metformin				
No use	82 (43.2)	960 (25.4)	1‡	1‡
<1	40 (21.1)	943 (25.0)	0.50 (0.34–0.73)	0.59 (0.39–0.90)
1–2	28 (14.7)	711 (18.9)	0.45 (0.29–0.71)	0.61 (0.37–0.99)
≥2	40 (21.1)	1158 (30.7)	0.37 (0.24–0.55)	0.52 (0.33–0.81)
p-value for trend			<0.001	0.003
Sulfonylureas				
No use	54 (28.4)	1320 (35.0)	1‡	1‡
<1	67 (35.3)	945 (25.1)	1.73 (1.20–2.50)	1.73 (1.15–2.60)
1–2	24 (12.6)	563 (14.9)	1.04 (0.64–1.71)	1.08 (0.63–1.85)
≥2	45 (23.7)	944 (25.0)	1.15 (0.75–1.74)	1.44 (0.90–2.29)
p-value for trend			0.861	0.323
Repaglinide				
No use	157 (82.6)	3475 (92.1)	1‡	1‡
<1	23 (12.1)	189 (5.0)	2.68 (1.69–4.26)	2.30 (1.39–3.83)
1–2	5 (2.6)	58 (1.5)	1.90 (0.75–4.83)	1.29 (0.47–3.51)
≥2	5 (2.6)	50 (1.3)	2.23 (0.88–6.65)	1.91 (0.70–5.23)
p-value for trend			<0.001	0.015

*Estimates from conditional logistic regression models, conditioned on sex, age, date at cohort entry, and duration of follow-up.
†Estimates further adjusted for Charlson's comorbidity index, cardio/cerebrovascular diseases, use of antipertensive drugs, use of antiplateletes drugs, use of statins (in the 5 years before cohort entry), and for use of other antidiabetics (during follow-up).
‡Reference category.

found an inverse association between metformin and HCC.[8–16,21] Moreover, several studies also reported direct associations with insulin,[8,9,14,20] sulfonylureas[8,9,14,21] and repaglinide.[14,17] A few studies suggested that TZD may have a beneficial effect on HCC,[9,12,17–19] while data are scantier with reference to other hypoglycemic drugs.[12,18]

The anti-neoplastic activity of metformin has been related to reduced insulin resistance and weight loss.[29–31] Insulin-independent mechanisms on the process of carcinogenesis have also been implicated, since metformin has been shown to inhibit global protein synthesis and proliferation in various cancer cell lines, by activation of adenosine monophosphate–activated protein kinase and consequent inhibition of the mammalian target of rapamycin signaling and protein synthesis.[30,32–34]

On the other hand, insulin and insulin secretagogues that stimulate endogenous insulin release (as sulfonylureas or glinides) can promote (liver) carcinogenesis by increasing insulin-like growth factor-1 activity, stimulating hepatic cell proliferation, and affecting cell metabolism.[35–37]

Severity of diabetes and variable baseline characteristics of diabetic patients may, however, have influenced the choice of antidiabetics and the subsequent risk of developing HCC. Metformin is a first-line antidiabetic drug prescribed in less severe/shorter diabetes, and in pre-diabetes, too, while insulin is prescribed to patients with longer and more advanced diabetes, which in turn may be associated with higher risk of HCC.[38] Although in general the presence of liver diseases has little implication in the choice of specific treatments for diabetes, attention should be paid to the prescription of antidiabetic drugs among patients with advanced hepatic diseases.[39] For example, there are indications that metformin should be used with caution in patients with impaired liver function. Thus, confounding by indication[40] may explain—at least in part—the observed associations between selected antidiabetic drugs and HCC risk.

The significant duration–risk relationship with insulin points to a real role of insulin in the development of HCC, although the over two-fold excess risk observed for use for less than 1 year suggests that diabetic patients under insulin treatment have a higher background rate of HCC, probably related to their diabetes severity. The same line of reasoning applies when looking at the duration–risk relation with metformin, and particularly with sulfonylureas and glinidis.

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The interpretation of the associations with single antidiabetic drug class is also made complex by the fact that several diabetic patients use multiple antidiabetics simultaneously, and consequently, the comparison group for each individual antidiabetic includes other hypoglycemic drugs. In our study, it was not possible to identify a common reference group of untreated diabetic patients in order to overcome this problem, as previously proposed,[16] but our analyses accounted for concomitant use of different glucose-lowering drugs.

This study has some of the inherent limitations of the investigations based on healthcare utilization databases. First, the definition of the cohort of diabetic subjects was made on the basis of antidiabetic drug prescription, thus some misclassification is possible. However, the prevalence of diabetes in our cohort (about 3.9% in 2005–2007) is consistent with that reported in the study area[24]; moreover, the choice to consider only subjects over 40 years of age and exclude sporadic users should have limited the inclusion of type 1 as well as pregnancy-related diabetes. We also did not have measures of severity of diabetes (such as fasting blood glucose or hemoglobin A1c), but we matched cases and controls on follow-up duration, which has been shown to be as a proxy of diabetes severity.[41,42] Second, possible misclassification or measurement error in drug exposure was possible, because drug exposure was assessed through healthcare utilization data and patients may have failed to take the prescribed drugs. Such misclassification is in any case likely to be non-differential, and therefore, it should tend to bias the results towards the null. Third, identification of cancer cases from healthcare utilization databases may have been suboptimal, and we did not have histological/pathological data to confirm HCC diagnosis and establish tumor grade and stage. Thus, it is possible that we included some secondary/metastatic tumors cases, although our criteria of inclusion in the cohort were quite stringent in order to limit this possibility. Lombardy was not covered by an integrated Cancer Registry System to confirm the accuracy of our cancer diagnoses, but a study on administrative heath databases from the Lombardy region, which compared cancer cases identified in those databases with those reported in a Cancer Registry of the study area, found a high positive predictive value (>95%) for major neoplasms.[43] The higher rate of HCC in our diabetic cohort than that reported in other similar cohorts[44,45] may reflect the higher baseline rate of HCC in this Italian population as compared with other (northern) European countries.[46] Finally, we lacked valid information on various possible confounding variables, including lifestyle factors (such as body mass index, alcohol, and tobacco), family history of cancer, hepatitis, cirrhosis, and alcohol dependence.[47] However, it is unlikely that most of these factors were differentially distributed between ever and never users of various antidiabetic drugs, thus confounding is unlikely to have influenced the internal validity of our results. We were able to adjust our risk estimates for a few concomitant comorbidities, the Charlson's comorbidity index, and the use of selected drugs as proxy of the general health conditions of our diabetic population. This attenuated but did not totally explain the observed associations.

Among the strengths of our study, there are the large cohorts of diabetic patients including a relatively large number of HCC cases as compared with other non Asian-studies; we also chose to match 20 controls per case in order to increase statistical power, given the rarity of exposure of some antidiabetic drugs.[27] The study was population-based and had a prospective design, thus minimizing possible selection and recall bias. It was based on healthcare utilization databases, which likely included valid information on practically all prescriptions, for antidiabetic drugs, because they are reimbursed by the Italian NHS. Moreover, our study included only new antidiabetic users, thus having the possibility to investigate the relation with duration of various antidiabetic drugs.[48]

In conclusion, our study gives some support to the evidence that diabetic patients using metformin and possibly other antidiabetic drugs that increase insulin sensibility (such as TZD) have a reduced risk of HCC, while those using drugs that increase circulating insulin, such as exogenous insulin, or insulin secretagogues, have an increased risk. These results thus point at the modulation of insulin level as a relevant factor in the development of HCC in diabetic patients.[49] Whether these associations are causal, or influenced by different severity of diabetes and/or possible residual bias or misclassification, is still open to discussion.

CONFLICT OF INTEREST

C. L. V. received honoraria as member of Diabetes Advisory Board from SANOFI. G. C. took part in a variety of projects funded by the pharmaceutical industry (Novartis and GSK). He also received honoraria as member of Diabetes Advisory Board from Roche. All other authors declare no conflict of interest.

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KEY POINTS

- Drugs used for the diabetes treatment may modulate hepatocellular carcinoma risk.
- Metformin, and possibly other antidiabetic drugs that increase insulin sensibility, may reduce the risk of hepatocellular carcinoma.
- Insulin and other antidiabetic drugs that increase circulating insulin, such as insulin secretagogues, may increase its risk.

ETHICS STATEMENT

According to the rules from the Italian Medicines Agency, retrospective studies without direct contact with patients do not need a written consent to process personal data when they are used for research aims.

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