original article

Diabetes, Obesity and Metabolism 14: 23–29, 2012.

ORIGINAL ARTICLE

Cancer mortality reduction and metformin: a retrospective cohort study in type 2 diabetic patients

S. Bo[1], G. Ciccone[2], R. Rosato[2], P. Villois[1], G. Appendino[1], E. Ghigo[1] & G. Grassi[1]

[1]*Department of Internal Medicine, University of Torino, Turin, Italy*
[2]*Unit of Cancer Epidemiology CPO, S. Giovanni Battista Hospital, University of Torino, Turin, Italy*

Aims: Few studies suggest that metformin decreases cancer mortality in type-2 diabetic patients (T2DP). We explored the association between the type and duration of antidiabetic therapies and cancer and other-than-cancer mortality in a T2DP cohort, taking into account the competing risks between different causes of death and multiple potential confounding effects. The mortality rates were compared with the general population from the same area.

Methods: In 1995, all T2DP (n = 3685) at our diabetes clinic in Turin (~12% of all T2DP in the city), without cancer at baseline, were identified. Vital status was assessed after a mean 4.5-year follow-up.

Results: Metformin users had greater adiposity, while insulin users had more co-morbidities. All-cause- and cancer-related deaths occurred in: 9.2 and 1.6% of metformin users, 13.1 and 3.0% of sulfonylureas users and 26.8 and 4.8% of insulin users, respectively. In a Cox regression model for competing risks, adjusted for propensity score, metformin users showed a lower cancer mortality risk [hazard ratio (HR) = 0.56; 95% confidence interval (CI) 0.34–0.94], while insulin was positively associated with other-than-cancer mortality (HR = 1.56; 95%CI 1.22–1.99). Each 5-year metformin exposure was associated with a reduction in cancer death by 0.73, whereas every 5-year insulin exposure was associated with 1.25-fold increase in other-than-cancer death.

Standardized mortality ratios for cancer and other-than-cancer mortality in metformin users were 43.6 (95%CI 25.8–69.0) and 99.1 (95%CI 79.3–122.5), respectively, in comparison with the general population.

Conclusions: Metformin users showed a lower risk of cancer-related mortality than not users or patients on diet only; this may represent another reason to choose metformin as a first-line therapy in T2DP.

Keywords: cancer mortality, insulin, metformin, sulfonylureas, type 2 diabetes mellitus

Date submitted 6 March 2011; date of first decision 24 April 2011; date of final acceptance 16 July 2011

Introduction

Many epidemiological studies have shown that some cancers (pancreas, liver, colorectum, breast, endometrium) occur more commonly in patients with type 2 diabetes than in the general population, while other (prostate cancers) were slightly reduced [1]. Among cancer patients, pre-existing diabetes was associated with an increased risk of all-cause mortality with respect to subjects without diabetes, as recently shown by a meta-analysis of 23 population- and clinical-based studies [2]. It is unclear whether the increased mortality is a consequence of obesity or of the other impaired health conditions associated with diabetes—hyperglycaemia, hyperinsulinaemia and inflammation [3].

Some large cohort studies have reported lower cancer incidence and mortality in diabetic patients treated with metformin [4–11]. A recent meta-analysis concluded that metformin in diabetic patients is associated with a decreased risk of cancer incidence compared with other treatments, even if most studies were retrospective [12]. On the basis of plausible mechanisms and laboratory findings, metformin, an activator of the AMP-activated protein kinase (AMPK), has been suggested to improve cancer prognosis [3, 13]. Insulin, sulfonylureas and thiazolidinediones have been variably reported to have no effect or a slightly increasing or a significantly reducing effect on cancer risk [1, 10, 14, 15].

However, as recently discussed by a consensus report, many open research questions remain [16]. Observed associations between cancer risk and specific drugs may have been confounded by indications for treatment and by the complex progressive nature of hyperglycaemia and pharmacotherapy in type 2 diabetes mellitus, because most diabetic patients are treated with multiple hypoglycaemic agents, and require repeated treatment adaptations over time. Furthermore, specific drugs might be associated with other cancer risk factors, and confounding by unmeasured risk factors or conditions cannot be controlled. Finally, a long duration of exposure and latency may be required to affect carcinogenesis [16]. Therefore, assessing the independent contribution of hypoglycaemic drugs to cancer incidence through observational studies might be quite difficult. On the other hand, randomized controlled

Correspondence to: Simona Bo, Dipartimento di Medicina Interna, Universita' di Torino, Corso Dogliotti 14, 10126 Torino, Italy.
E-mail: sbo@molinette.piemonte.it

clinical trials are probably unlikely to be able to fully evaluate these associations, because of the length of follow-up, the large sample size and the cost required, and because of the high expected proportion of treatment crossover that would be needed to treat hyperglycaemia and the related complications [16].

We studied the effect of metformin treatment on cancer mortality by a retrospective cohort study of type-2 diabetic patients (T2DP) from a diabetic clinic. Sulfonylureas and insulin effects were also evaluated. We assessed the specific role of each drug by taking into account its frequently prescribed association and the possible competing risk between different causes of death. In addition, because multiple factors could have affected the treatment choice, a propensity score analysis was used to reduce the confounding effect by indication. We excluded patients with a cancer history at baseline, which might have heavily affected mortality.

Finally, the cause-specific mortality rates of the cohort were compared with expected figures from the general population.

Methods

Patients

All 3892 patients aged ≥35 years with type 2 diabetes who resided in Piedmont (north-western Italy) and attended the Diabetes Clinic of the San Giovanni Battista Hospital in Turin during 1995 and who were alive on 1 January 1996 were identified, as previously reported [17, 18]. Approximately 70% (n = 2678) lived in Turin, the largest city in the Piedmont Region. They represented approximately 12% of all T2DP in the city: 22,997 of 569,638 aged ≥35 years, which yielded a prevalence of 4.0%.

The definition of type 2 diabetes was based on age at diagnosis, type of treatment, C-peptide level [19] and, when available, β-cell auto-antibody negativity. Demographic data (age, sex, area of residence) and clinical data relative to the year 1995 [height, smoking, duration of disease, last three determinations of body weight, systolic and diastolic blood pressure, fasting glycaemia and glycated haemoglobin (HbA1c), type of antidiabetic treatment or other drugs and presence of chronic complications, cancer or other co-morbidity] were abstracted from clinical records. Patients provided their informed consent to their clinical data treatment. All procedures were in accordance with the Declaration of Helsinki.

Outcomes

The cohort was followed up for mortality from 1 January 1996 to 30 June 2000. Information on the vital status of each patient and the causes of death of the 599 who died (52.8% died in a hospital) was collected from the demographic files of the town of residence or death. Vital status was ascertained for 100% of the cohort, and the cause of death was obtained for 590 of the 599 who died. The underlying cause of death was derived from death certificates and coded according to the ICD-9 (International Classification of Diseases, Ninth Revision). The causes of death were coded by a single trained researcher, who was blinded to the patients' characteristics and therapies. Cancer deaths corresponded to ICD codes 140-239.

Methods

Weight and height were measured by nurses and reported in the clinical records. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. In 1995, hypertension was defined as systolic or diastolic blood pressure ≥140/90 mm Hg and/or current antihypertensive treatment [20]. Retinopathy was diagnosed by ophthalmoscopic examination and/or retinal photography; fundoscopy was performed by an ophthalmologist experienced in diabetic retinopathy. Patients with retinopathy (any degree) had a retinal photograph taken, according to the European protocol for diabetic retinopathy [21]. Nephropathy was established by the presence of microalbuminuria, gross proteinuria or elevated serum creatinine levels, according to the American Diabetes Association statements [22]. Impaired renal function was identified based on serum creatinine concentrations higher than 114.9 µmol/l for men and 106.1 µmol/l for women [18]. Coronary artery disease was established based on documented events recorded by a physician (angina, previous myocardial infarct, coronary artery by-pass graft or other invasive procedures to treat coronary artery disease). Peripheral artery disease was considered when conditions such as ischaemic foot ulcers, gangrene, amputation (as a result of ischemic gangrene), vascular surgery, transient ischaemic attacks, strokes, intermittent claudication, absent foot pulses or abnormal brachial or posterior tibial blood pressure on the basis of Doppler techniques were identified from clinical records. Cancer and other co-morbidities (chronic liver disease and chronic obstructive pulmonary disease) were established by the presence of documented pathologies recorded by a physician.

HbA1c was measured at each visit by ion-exchange chromatography applied to a high-performance liquid chromatography system (Menarini, Florence, Italy). At least three values were obtained for each patient, and the value reported is the mean of the final three values obtained in 1995.

Statistical analyses

To consider the effect of several potential confounders, a propensity score was initially derived from a multi-logit regression model used to predict the choice of treatment (eight categories of treatment, including each drug alone or in any possible combination) with all of the following variables: age (years), sex, diabetes duration (years), HbA1c (as a continuous variable), smoking (yes/no), BMI (as a continuous variable), presence (yes/no) of retinopathy, nephropathy, coronary or peripheral artery disease, other co-morbidities and the use (yes/no) of antihypertensive drugs and acetylsalicylic acid. This model defined the patients' specific propensity scores for each treatment. Then, two Cox regression models, one for all-cause and the other for specific-cause deaths, considered to be competing risks, were applied to estimate the probability of dying of any causes and of specific causes (cancer and other-than-cancer deaths), according to antidiabetic treatments,

adjusted for the estimated propensity score. Exposure duration to each drug was analyzed by a Cox regression model for competing risks and adjusted for the propensity score, to estimate the incremental risk of death for every 5 years of drug usage.

The Fine and Gray test was applied to estimate the effect of treatment on cause-specific cumulative incidence mortality.

The observed numbers of deaths during follow-up for the subgroup of diabetic patients residing in Turin (n = 2678, corresponding to 11081.8 person-years at risk) were compared with the expected numbers derived from the death rates of the whole population of Turin during the same period (January 1996–June 2000). Age- (in 5-year classes) and sex-standardized mortality ratios (SMR) (×100), were estimated as the ratio of observed to expected numbers of deaths. The 95%CIs of SMRs were computed using the chi-square approximation.

Results

At our institution, in 1995, metformin was prescribed as the first-line drug in obese patients, while sulfonylureas were given to normal weight/overweight patients and patients who did not reach their glycaemic goals or were intolerant to metformin. Other antidiabetic drugs, such as metiglitinides, thiazolidinediones, glucagon-like peptide 1 analogues, dipeptidyl peptidase-4, and amylin analogues, were not yet used.

From the cohort of T2DP (n = 3892), 68% of the patients were treated with sulfonylureas, 40% with metformin (34% with both drugs), 26% with insulin and 9.9% with insulin alone. Of the last group, approximately 70% had chronic renal or liver impairment or other contraindications to oral hypoglycaemic agents, while 30% showed possible secondary failure to oral agents, with normal C-peptide levels and negative β-cell auto-antibody levels.

Patients with a history of cancer at baseline (n = 207) were excluded; thus data for 3685 individuals were analyzed. Patients on diet only accounted for 16.8% of the sample, those treated with metformin only, sulfonylureas only, insulin only and different combinations of these drugs made up 4.8, 26.2, 9.5 and 42.6% of the sample, respectively. Table 1 summarizes the baseline characteristics of the cohort grouped by hypoglycaemic treatment. The patients were divided according to the use or non-use of metformin, sulfonylureas or insulin. Insulin-treated patients were more likely to show chronic complications and co-morbidity, while patients on metformin had less co-morbidity but greater adiposity.

All-cause (total n = 535) mortality occurred more frequently in insulin-treated patients, while cancer mortality (total n = 122) was the lowest in individuals treated with metformin (Table 2). Sulfonylureas users displayed an intermediate profile.

Figures 1 and 2 show, respectively, the cumulative incidence for cancer-related and other-than-cancer mortality in patients treated with metformin as compared with those not treated with metformin. Metformin users showed a significantly lower probability of both causes of death.

Cox regression models for competing risk revealed a statistically significant reduction in all-cause- and cancer-related

Table 1. Baseline characteristics of the cohort, according to hypoglycaemic treatment.

	Diet only	Metformin	Sulfonylureas	Insulin
Number	620	1479	2511	944
Age (years)	66.9 ± 11.1	67.6 ± 8.9	70.3 ± 9.8	71.8 ± 10.2
Males (number; %)	376; 60.7	719; 48.6	1260; 50.2	416; 44.1
Diabetes duration (years)	6.7 ± 7.5	13.0 ± 8.0	12.5 ± 8.2	16.6 ± 8.3
BMI (kg/m^2)*	28.2 ± 4.6	29.3 ± 5.0	28.1 ± 4.6	27.7 ± 4.5
HbA1c (%)	6.7 ± 1.5	8.4 ± 1.4	8.2 ± 1.5	8.8 ± 1.4
Smoking (number; %)	151; 24.3	313; 21.2	522; 20.8	205; 21.7
Systolic BP (mmHg)	144.0 ± 17.8	148.6 ± 15.9	148.1 ± 16.1	148.9 ± 16.3
Diastolic BP (mmHg)	83.6 ± 9.3	83.7 ± 8.2	83.0 ± 8.1	82.1 ± 7.9
Antihypertensive therapy (number; %)	269; 43.4	687; 46.5	1146; 45.6	459; 48.6
Statins (number; %)	24; 3.9	79; 5.3	113; 4.5	47; 5.0
Aspirin (number; %)	99; 16.0	201; 13.6	406; 16.2	186; 19.7
Hypertension (number; %)	431; 69.5	1160; 78.4	1928; 76.8	748; 79.2
Metformin (number; %)	—	1479; 100	1276; 50.8	325; 34.4
Sulfanylureas (number; %)	—	1276; 86.3	2511; 100	568; 60.2
Insulin (number; %)	—	325; 22.0	568; 22.6	944; 100
Retinopathy (number; %)†	98; 15.8	510; 34.5	788; 31.4	460; 48.7
Nephropathy (number; %)	176; 28.4	529; 35.8	880; 35.1	499; 52.9
Impaired renal function (number; %)	16; 2.6	17; 1.2	84; 3.4	119; 12.6
Coronary artery disease (number; %)	57; 9.2	161; 10.9	323; 12.9	152; 16.1
Peripheral artery disease (number; %)	47; 7.6	99; 6.7	238; 9.5	151; 16.0
Cirrhosis (number; %)	17; 2.7	6; 0.4	35; 1.4	53; 5.6
COPD (number; %)	15; 2.4	27; 1.8	60; 2.4	34; 3.6

BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease.
Mean ± SD or number; percentages.
*Missing data = 43.

Table 2. Deaths for all-cause and cancer causes, according to hypoglycaemic treatment.

	Diet only	Metformin	Sulfonylureas	Insulin
Number	620	1479	2511	944
All causes (number; %)	68; 11.0	136; 9.2	328; 13.1	253; 26.8
Cancer (number; %)	26; 4.2	23; 1.6	74; 3.0	45; 4.8

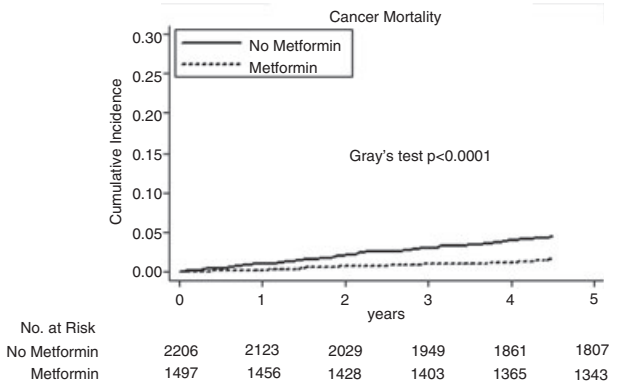

Figure 1. Cumulative incidence for cancer mortality in patients treated with metformin with respect to those not treated with metformin.

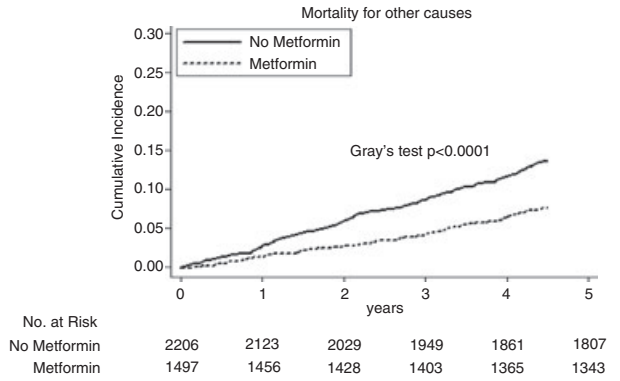

Figure 2. Cumulative incidence for other-than-cancer mortality in patients treated with metformin with respect to those not treated with metformin.

mortality in metformin users (Table 3). In a multivariate model, adjusted for propensity score, metformin users were confirmed to be at a much lower risk of cancer mortality (Table 3). A respectively increased or reduced risk of all-cause mortality and other-than-cancer mortality was found in patients treated with insulin or sulfonylureas in the multivariate models, while no association between cancer mortality and insulin or sulfonylureas use was evident (Table 3). Each 5-year metformin exposure was significantly associated with a reduction in cancer death by 0.73, whereas every 5-year insulin exposure was associated with a 1.25-fold increase in other-than-cancer death (Table 4). No statistically significant interactions between drugs were detected.

Data did not change significantly after excluding patients with impaired renal function (n = 188; 5.1%), cirrhosis (n = 99; 2.7%) or chronic obstructive pulmonary disease (n = 89; 2.4%) from the survival analyses.

A sex- and age-standardized comparison with the mortality of the general population was performed for the subgroup of patients who resided in Turin (n = 2678), with and without cancer at baseline (Table 5). The risk for all-cause mortality was significantly reduced in metformin users compared with the general population, which was mainly due to the reduced cancer-related mortality (SMR = 43.6; 95%CI 25.8–69.0), while other-than-cancer mortality was not different. Sulfonylureas users showed significantly lower SMRs for both cancer and other-than-cancer mortality, contrary to insulin users, whose mortality risks were significantly increased.

Table 3. Survival analysis for all-cause, cancer and other-than-cancer mortality, crude and adjusted for propensity score, according to hypoglycaemic treatment.

	Crude			Adjusted		
	HR	95% CI	p	HR*	95% CI	p
All-cause mortality						
Diet only	1			1		
Metformin	0.51	0.41–0.62	<0.001	0.79	0.63–0.99	0.04
Sulfonylureas	0.98	0.82–1.18	0.85	0.78	0.64–0.96	0.02
Insulin	2.79	2.36–3.32	<0.001	1.51	1.22–1.88	<0.001
Cancer mortality						
Diet only	1			1		
Metformin	0.34	0.21–0.54	<0.001	0.56	0.34–0.94	0.02
Sulfonylureas	1.00	0.68–1.46	0.99	0.76	0.50–1.17	0.21
Insulin	1.79	1.24–2.60	0.002	1.41	0.88–2.25	0.16
Other-than-cancer mortality						
Diet only	1			1		
Metformin	0.57	0.45–0.71	<0.001	0.86	0.67–1.11	0.25
Sulfonylureas	0.97	0.79–1.20	0.80	0.78	0.62–0.99	0.04
Insulin	3.17	2.61–3.85	<0.001	1.56	1.22–1.99	<0.001

CI, confidence interval; HR, hazard ratio.
*Adjusted for propensity score.

Table 4. Survival analysis for all-cause, cancer and other-than-cancer mortality, crude and adjusted for propensity score, according to duration of exposure (in 5-year classes) to hypoglycaemic treatment.

	Crude			Adjusted		
	HR	95% CI	p	HR*	95% CI	p
All-cause mortality						
Metformin	0.82	0.77–0.87	<0.001	0.91	0.85–0.96	<0.001
Sulfonylureas	1.03	0.96–1.09	0.44	0.95	0.90–1.01	0.11
Insulin	1.41	1.32–1.51	<0.001	1.13	1.04–1.23	<0.001
Cancer mortality						
Metformin	0.64	0.54–0.76	<0.001	0.73	0.61–0.88	<0.001
Sulfonylureas	1.02	0.90–1.16	0.71	0.97	0.85–1.12	0.69
Insulin	1.29	1.11–1.51	0.001	1.14	0.96–1.36	0.13
Other-than-cancer mortality						
Metformin	0.86	0.81–0.92	0.001	0.94	0.88–1.01	0.11
Sulfonylureas	1.02	0.96–1.10	0.51	0.95	0.88–1.01	0.10
Insulin	1.44	1.34–1.56	<0.001	1.25	1.15–1.35	<0.001

CI, confidence interval; HR, hazard ratio.
*Adjusted for propensity score.

Table 5. Standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) estimated for the cohort of patients with type 2 diabetes resident in Turin (n = 2678) with respect to the general population, by age and sex.

	Observed no deaths	Expected no deaths	SMR	95%CI
All-cause mortality				
Diet only	59	72.9	80.9	61.6–104.4
Metformin	104	128.0	81.2	66.4–98.4
Sulfonylureas	248	321.6	77.1	67.8–87.3
Insulin	200	122.2	163.7	141.8–188.1
All	428	455	94.1	85.4–103.4
Cancer mortality				
Diet only	18	20.8	86.6	51.2–137.1
Metformin	18	41.3	43.6	25.8–69.0
Sulfonylureas	64	87.8	72.9	56.1–93.2
Insulin	48	30.8	156.1	115.0–207.1
All	112	123.8	90.5	74.5–108.9
Other-than-cancer mortality				
Diet only	41	52.2	78.6	56.4–106.7
Metformin	86	86.7	99.1	79.3–122.5
Sulfonylureas	184	233.8	78.7	67.7–90.9
Insulin	152	91.4	166.3	140.9–195.0
All	316	328.6	96.2	85.8–107.4

Risks in patients on diet only did not significantly differ from the general population of the same area.

Discussion

These results, derived from a large cohort of T2DP, after a 4.5-year follow-up, add further evidence to the protective effect of metformin treatment in reducing the risk of cancer mortality. Insulin users are at increased risk for all-cause and other-than-cancer death. The mortality profile for sulfonylureas is more complex to interpret. The risk for cancer death was greatly reduced in metformin users, in a standardized comparison with the general population from the same area.

Metformin reduced the risk for cancer in type 2 diabetes, with a dose–response relationship, and a 37% lower adjusted cancer incidence was found [4–11]. In our patients, metformin use almost halved the risk of cancer mortality, as determined by a multivariate model, adjusted for propensity score. The risk was reduced with an HR of 0.73 for every 5-year of drug use, and its survival benefit for each 1-year follow-up was significant (figure 1). One can hypothesize that metformin is primarily used as a first-line therapy in less complicated patients. In our patients, metformin users were indeed younger and had less co-morbidity. Nevertheless, they did not display a significant difference in other-than-cancer death, with lower total mortality specifically due to cancer death only. Furthermore, they displayed an increased adiposity, a condition clearly predisposing patients to higher death rates for most cancers: it has been calculated that more than 90,000 cancer deaths per year may be prevented by maintaining a normal BMI throughout life [23]. Finally, cancer mortality was even lower in metformin users than in patients on diet only, whose baseline clinical characteristics (age, HbA1c, diabetes duration, BMI) seemed more favourable (Table 1). This suggests that adding metformin conferred an independent and specific protective benefit.

Metformin exerts its effects by activating the AMPK, a major cellular regulator of lipid and glucose metabolism, that acts on aberrant cancer cellular growth by inhibiting the mTOR pathway, which may in turn regulate cell proliferation [24, 25]. Metformin could disrupt the cross talk between insulin receptors and G-protein coupled receptors and block the mitogenic effects of insulin and insulin-like growth factor 1 at post-receptor levels. Other non-AMPK-dependent mechanisms potentially responsible for the antineoplastic action may be: p53 activation, downregulation of cyclin D1, blocking the cell cycle in the G_0/G_1 phase, inhibition of the unfolded response (a survival mechanism of the cell) and suppression of HER2 oncoprotein expression [25, 26].

This drug is associated with a reduced incidence of cancer in laboratory animals, and it inhibits the growth of human breast cancer cells [1, 23]. Metformin is actually being evaluated as an adjuvant therapy in breast cancer trials, because it seems to enhance chemotherapy and yields higher pathologically complete response rates [13, 27].

Finally, we found lower cancer mortality in our patients treated with metformin as compared with the general population, contrary to many epidemiological studies [1, 2, 8], but in line with others [28, 29]. Intriguingly, Landman found that the mortality of patients taking metformin was comparable to that of the general population, while diabetic patients who were non-taking metformin displayed an increased cancer mortality ratio [8]. Compared with our study, those patients experienced a reduced mean diabetes duration (5–7 years); thus, they might be less exposed to the protective effect of metformin. Accordingly, this drug appeared to be more beneficial in longer trials in a meta-analysis of metformin effects on cardiovascular events and mortality [30] and we found a significant inverse association between the duration of drug exposure and cancer-related death.

Insulin is a growth-promoting hormone with mitogenic effects. Insulin may bind and activate IGF-1 receptors, which have much more potent mitogenic and transforming activity than the insulin receptors. Furthermore, many cancer cells have an increased content of insulin receptors, or post-receptor molecular mechanisms may be implicated [1]. Thus, it is not surprising that antidiabetic therapies that reduce insulin resistance and the associated changes in adipokine levels might play a role in the relationship between type 2 diabetes and cancer. Metformin reduced insulin levels in non-diabetic hyperinsulinaemic women with early-stage breast cancer by 22% [31]. This effect might have been implicated in our overweight diabetic cohort and could justify why patients on diet only, who presumably had not yet progressed to β-cell failure with decreased insulin levels, showed a higher cancer-related mortality than patients on hypoglycaemic agents. In our cohort, an increase in other-than-cancer mortality was significantly associated with insulin use and the length of exposure (particularly cardiovascular deaths; data not reported), but cancer-related mortality was not. Indeed, compared with the general population, insulin

increased the risk of cancer mortality (Table 5). This is a debated topic with conflicting results. Previous studies have shown an increased cancer risk for insulin users [7, 8]. Recent data show that insulin usage not only fails to predispose patients to cancer, but also strongly reduces the cancer risk by lowering blood glucose, oxidative stress and inflammation, all conditions that predispose diabetic patients to cancer [14].

A survival benefit for other-than-cancer death, but not for cancer, was observed in our patients taking sulfonylureas (Tables 3 and 4), while, when compared them to the general population, treatment with these drugs significantly reduced both mortality rates (Table 5). Literature on this topic is highly controversial. No effect [5, 10] or an increased [6, 7, 32] or a reduced risk of cancer-related mortality [15] have been reported. A possible explanation for this discrepancy might be the differential effects of individual sulfonylureas: glipizide or glibenclamide is associated with increased cancer incidence, while gliclazide shows a protective effect, probably because of its extra-glycaemic effects of DNA protection from chemical or radiation damage [15, 33].

Thus, antidiabetic drugs may greatly affect survival rates. Accordingly, patients on diet only did not display any difference in the mortality ratios with respect to the general population.

Data about the effects of thiazolidinediones and α-glucosidase inhibitors on cancer mortality are scarce, even though the former have been associated with either an increased [10] or diminished risk of cancer [34].

Limitations and Strengths

We recognize the limitations of our observational study. We adjusted the analyses for many potential confounders, including co-morbidity and chronic complications, but residual confounding cannot be excluded. It is unlikely, however, that residual confounding accounts for the entire reduction in the risk of cancer death (47%). Many diabetic patients take different types of hypoglycaemic drugs during the course of the disease and we do not know if patients were changing therapy during the follow-up. However, this type of misclassification could have rather reduced the association found.

Because our cohort comprised patients with different times of onset of diabetes, the duration of diabetes and its complications were carefully considered in the analyses, although a selection effect of patients with longer disease duration was unavoidable. We cannot exclude the possibility that attending a diabetic clinic might confer some advantage for the control of major health problems with respect to the general population. Nevertheless, our cohort represented approximately 12% of all patients with type 2 diabetes in Turin, with similar age and sex distribution, as residence in Turin was the main determinant of the catchment area [17, 18]. The number of cases was insufficient to perform separate analyses for neoplasm type; furthermore dose or type of insulin or sulfonylureas could not be examined.

Patients with impaired renal function are at increased risk for cancer [35] and were underrepresented in the metformin-treated group, because this is a contraindication to metformin use. Nevertheless, after excluding these subjects from the analyses, the data did not change significantly.

The strengths of the study include: an analysis of cancer and other-than-cancer mortality by a competing risks model, considering the effect of multiple potential confounders through use of a propensity score; the exclusion of patients with a cancer history at baseline, which might have heavily affected mortality; and the comparison with individuals from the general population from the same area.

Conclusion

Metformin therapy is associated with lower cancer mortality than that seen in patients on diet or not treated with this drug, thus providing additional evidence for choosing this drug as the first-line therapy in type 2 diabetes mellitus.

Acknowledgements

This study was supported by a grant from Regione Piemonte, Ricerca Sanitaria Finalizzata 2009.

Conflict of Interest

S. B. and G. G. participated in the conception of the study. S. B., E. G. and G. G. participated in design of the study. S. B. participated in supervision of data collection. S. B., G. C. and R. R. participated in data analysis. S. B., G. C., R. R., P. V., G. A., E. G. and G. G. participated in interpretation of the findings of the study. S. B., E. G. and G. G. participated in manuscript writing. S. B., G. C., R. R., P. V., G. A., E. G. and G. G. participated in manuscript revision.

The authors do not declare any conflict of interest relevant to this manuscript.

References

1. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009; **16**: 1103–1123.
2. Barone BB, Yeh HC, Snyder CF et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus. JAMA 2008; **300**: 2754–2764.
3. Duncan BB, Schmidt MI. Metformin, cancer, alphabet soup, and the role of epidemiology in etiologic research. Diabetes Care 2009; **32**: 1748–1750.
4. Evans JMM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. Br Med J 2005; **330**: 1304–1305.
5. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JMM. New users of metformin are at low risk of incident cancer. Diabetes Care 2009; **32**: 1620–1625.
6. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009; **52**: 1766–1777.
7. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006; **29**: 254–258.
8. Landman GWD, Kleefstra N, van Hateren KJJ, Groenier KH, Gans ROB, Bilo HJG. Metformin associated with lower cancer mortality in type 2 diabetes. Diabetes Care 2010; **33**: 322–326.

9. Bosco JL, Antonsen S, Sørensen HT, Pedersen L, Lash TL. Metformin and incident breast cancer among diabetic women: a population-based case-control study in Denmark. Cancer Epidemiol Biomarkers Prev 2011; **20**: 101–111.
10. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010; **33**: 1304–1308.
11. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer 2011; **11**: 20.
12. Decensi A, Puntoni M, Goodwin P et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res 2010; **3**: 1451–1461.
13. Jiralerspong S, Palla SL, Giordano SH et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009; **27**: 3297–3302.
14. Yang X, Ko GTC, So WY et al. Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes 2010; **59**: 1254–1260.
15. Yang X, So WY, Ma RCW et al. 2010; **90**: 343–351.
16. Giovannucci E, Harlan DM, Archer MC et al. Diabetes and cancer. A consensus report. CA Cancer J Clin 2010; **60**: 207–221.
17. Bo S, Ciccone G, Grassi G et al. Patients with type-2 diabetes have higher rate of hospitalisation than the general population. J Clin Epidemiol 2004; **57**: 1196–1201.
18. Bo S, Ciccone G, Rosato R et al. Renal damage in patients with type 2 diabetes: a strong predictor of mortality. Diabet Med 2005; **22**: 258–265.
19. Abraira C, Emanuele N, Colwell J et al, for VA Cooperative Study Group. Glycemic control and complications in type II diabetes: design of a feasibility trial. Diabetes Care 1992; **15**: 1560–1571.
20. Joint National Committee. The fifth report of the Joint National Committee on detection, evaluation and treatment of high blood pressure. Arch Intern Med 1993; **153**: 154–183.
21. Retinopathy Working Party. A protocol for screening for diabetic retinopathy in Europe. Diabetic Med 1991; **8**: 263–267.
22. American Diabetes Association. Diabetic nephropathy. Diabetes Care 2001; **24**: S69–S72.
23. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity and mortality from cancer in a prospectively studied cohort of US adults. New Engl J Med 2003; **348**: 1625–1238.
24. Zhou G, Myers R, Li Y et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001; **108**: 1167–1174.
25. Wang W, Guan KL. AMP-activated protein kinase and cancer. Acta Physiol 2009; **196**: 55–63.
26. Kourelis TV, Siegel RD. Metformin and cancer: new applications for an old drug. Med Oncol 2011 [Epub ahead of print].
27. Goodwin PJ, Ligibel JA, Stambolic V. Metformin in breast cancer: time for action. J Clin Oncol 2009; **27**: 3271–3273.
28. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and risk of cancer death in the Unites States. Am J Epidemiol 2003; **157**: 1092–1100.
29. De Giorgio R, Barbara G, Cecconi A, Corinaldesi R, Mancini AM. Diabetes is associated with longer survival rates in patients with malignant tumors. Arch Intern Med 2000; **160**: 2217.
30. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2011; **13**: 221–228.
31. Goodwin PJ, Pritchard KI, Ennis M. Insulin-lowering effects of metformin in women with early breast cancer. Clin Breast Cancer 2008; **8**: 501–505.
32. Li D, Yeung SCJ, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009; **137**: 482–488.
33. Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E. Sulphonylureas and cancer: a case-control study. Acta Diabetol 2009; **46**: 279–284.
34. Govindarajan R, Ratnasinghe L, Simmons DL et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol 2007; **25**: 1476–1481.
35. Wong G, Hayen A, Chapman JR et al. Association of CKD and cancer risk in older people. J Am Soc Nephrol 2009; **20**: 1341–1350.