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The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients

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ABSTRACT

Studies have shown an association between diabetes and cancer in Western countries; but this, as well as the influence of associated metabolic factors, must be confirmed by a prospective study in other population groups. This study aimed to investigate whether the strong association of cancer and diabetes is independent from the influence of hypertension, dyslipidemia, and gout in the Taiwanese population. A total of 985 815 study subjects were identified from the National Health Insurance in 1997 and followed up from 1998 to 2009. The demographic characteristics between patients with diabetes and cancer, including age, sex, hypertension, dyslipidemia, and gout, were analyzed using the χ^2 test. Cox proportional hazard regression models were used to determine the independent effects of diabetes on the risks of cancer. A total of 104 343 diabetic patients were followed up from 1998 to 2009. After adjusting for sex, age, hypertension, dyslipidemia, and gout, the incidences of cancer at any site and in the liver, colon, lungs, and prostate in diabetic patients were independently higher, with risk ratios of 1.56 (95% confidence interval [CI], 1.43-1.71), 1.67 (95% CI, 1.39-2.01), 1.75 (95% CI, 1.49-2.06), 1.54 (95% CI, 1.26-1.88), and 1.56 (95% CI, 1.19-2.04), respectively. Only breast cancer did not show any clinical significance. There was an increased incidence of cancer at any site in the diabetic patients compared with nondiabetic subjects. The most common cancers were liver, colon, lung, breast, and prostate cancer; and except for breast cancer, their incidences increased independently of hypertension, dyslipidemia, and gout in patients with diabetes.

1. Introduction

Diabetes and cancer are 2 common severe chronic diseases that lead to many deaths. Several studies have suggested that diabetes significantly increases the risk for different cancers. Today, there are more than 250 million people with diabetes worldwide; and this number is expected to reach 380 million in 20 years [1]. Thus, the association between diabetes and cancer

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is of clear importance. Diabetes and cancer are multifactorial, especially diabetes, which is a complex disease with a host of associated metabolic and hormonal derangements characterized by hyperglycemia, obesity, hypertension, dyslipidemia, and gout [2]. To date, the link between diabetes and cancer has not been widely studied and is not well understood.

Most of the previous studies were conducted with a case-control design, and many of them had a limited number of study subjects [1]. Some experts suggest that cancer incidence in diabetes may be related to its risk factors such as age, sex, race or ethnicity, overweight or obesity, diet, physical activity, tobacco smoking, alcohol, and metabolic syndrome [2]. However, the independent association of diabetes with related metabolic derangements (ie, hypertension, dyslipidemia, and gout) and the increased risk of cancer has not been widely studied. This study aimed to explore the association between cancer and diabetes, and the influence of hypertension, dyslipidemia, and gout on this association using a large nationally representative diabetic cohort selected from National Health Insurance (NHI).

2. Methods

2.1. Study population

The NHI program was implemented in Taiwan in 1995; and it offers a comprehensive, unified, and universal health insurance program to all citizens. All citizens with a registered domicile for at least 4 months in the Taiwan area should be enrolled. The coverage provides outpatient service, inpatient care, Chinese medicine, dental care, childbirth, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illnesses. The coverage rate was 96.16% of the whole population in 2000 but rose to 99% at the end of 2004 [3]. The state-run Bureau of National Health Insurance (BNHI) had contracted with 97% of hospitals as well as 90% of clinics all over the island. The BNHI accumulates all administrative and claims data for Taiwan, and the National Health Research Institute cooperates with the BNHI to establish an NHI research database that provided us 1 000 000 random subjects and that accumulates information of all beneficiaries, including personal identification number (PIN), date of birth, sex, geographic area of each member's NHI units, and date of enrollment and withdrawal between March 1995 and December 2009 [3]. There were no statistically significant differences in age, sex, and average insured payroll-related amount in all enrollees. For the precision of the claim data, the BNHI performs expert reviews on a random sample of every 50 to 100 ambulatory and inpatient claims in each hospital and clinic quarterly. Because the claim data included both inpatients and ambulatory patients, we believed that this recruitment procedure would not be biased in selecting sicker or healthier patients. Although it was not easy to specify the sensitivity and specificity of this approach, including the disease duration, both were believed to be good because the clinical settings tended to report all cases of diabetes in the claims data to ensure full reimbursement and because a false report of diagnosis would incur a severe penalty from the BNHI. With ethical approval from the National Health Research Institute, we used data from the ambulatory care claims, all inpatient claims, and an updated registry of beneficiaries from 1998 to 2009 that was funded by the Department of Internal Medicine, Kaohsiung Medical University Hospital, for this study. All NHI data sets can be interlinked with each individual PIN.

The diagnosis coding of the NHI in Taiwan is according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*), *Clinical Modification* diagnostic criteria. Diabetic care claims record patients with diabetes-related diagnoses with *ICD-9* code 250 (excluding type 1 diabetes mellitus with *ICD-9* code 2501). An individual was classified as a diabetic patient if she or he had an initial diabetes-related diagnosis at any time in 1997 and then had at least one service claim for either ambulatory or inpatient care within the subsequent 12 months. The diagnosis of diabetes was further confirmed by treatment at baseline prescribed by validated physicians that included 2 or more monthly packs of hypoglycemic medications. To detect newly diagnosed cancer cases, we excluded those patients diagnosed for any types of cancer (*ICD-9*: 140-208) during 1997-1998 from our diabetic group. The final diabetic cohort consisted of 104 343 patients. The index date for patients in the diabetic group was the date of their first outpatient visit for diabetes care in 1997.

2.2. Study end points

The ambulatory and inpatient claims include the records of all hospitalizations and provide various pieces of information, including PIN, date of birth, sex, date of admission and discharge, a maximum of 5 leading diagnoses and 4 operation codes, partial amount of expenses paid by the beneficiaries for the admission, and so forth. With the unique PIN, we linked study subjects in both diabetic and nondiabetic groups to the ambulatory and inpatient claims data from 1999 to 2009 to identify, if any, the first episode of primary or secondary diagnoses of any types of cancer (*ICD-9*: 140-208) as the end points of this study. In Taiwan, BNHI issues major illness/injury certificates/catastrophic illness cards to all patients with cancer; and these patients are exempt from copayment to the NHI if they are admitted or visited ambulatory for the illness associated with the related cancer. For the accuracy of the diagnoses of cancer, we retrieved only those patients using major illness/injury certificates/catastrophic illness cards for that particular admission. The study period was from January 1, 1999, to December 31, 2009, an 11-year-period.

2.3. Possible associated risk factors of diabetes and cancer

We identified possible associated risk factors for diabetes and cancer (hypertension [*ICD-9*: 4019], dyslipidemia [*ICD-9*: 272], and gout [*ICD-9*: 274]) from ambulatory and inpatient claims (1997-2009). We counted the above possible associated risk factors occurring in individuals in both groups only when the dates of diagnosis for the selected illnesses (possible associated risk factors) were noted before or on the day on which the study subjects were diagnosed with diabetes. The study subjects who had at least one service claim for either ambulatory or inpatient care within the subsequent 12 months with a primary diagnosis of hypertension, dyslipidemia, or gout without any types of cancer were identified in 1997. The diagnoses of hypertension, dyslipidemia, and gout were

Table 1 – Cancer incidence in subjects with and without diabetes

Cancer site	*ICD-9* code	Total (n = 985 815)			Male (n = 488 778)			Female (n = 497 037)		
		Total no. of cases	Without DM (%) (n = 881 472)	With DM (%) (n = 104 343)	Total no. of cases	Without DM (%) (n = 438 919)	With DM (%) (n = 498 59)	Total no. of cases	Without DM (%) (n = 442 553)	With DM (%) (n = 54 484)
Liver	155	5964	4317 (0.49)	1647 (1.58)*	3594	2631 (0.60)	963 (1.93)*	2370	1686 (0.38)	684 (1.26)*
Colon	153	6702	5117 (0.58)	1585 (1.52)*	3553	2736 (0.62)	817 (1.64)*	3149	2381 (0.54)	768 (1.41)*
Lung	162	4477	3188 (0.36)	1289 (1.24)*	2777	1964 (0.45)	813 (1.63)*	1700	1224 (0.28)	476 (0.87)*
Breast	174	3992	3386 (0.38)	606 (0.58)*	81	72 (0.02)	9 (0.02)	3911	3314 (0.75)	597 (1.10)*
Prostate	185	2205	1559 (0.18)	646 (0.62)*	2205	1559 (0.36)	646 (1.30)*			
Rectum	154	2552	1958 (0.22)	594 (0.57)*	1432	1122 (0.26)	310 (0.62)*	1120	836 (0.19)	284 (0.52)*
Stomach	151	1839	1445 (0.16)	394 (0.38)*	1038	798 (0.18)	240 (0.48)*	801	647 (0.15)	154 (0.28)*
Bladder	188	1463	1114 (0.13)	349 (0.33)*	899	684 (0.16)	215 (0.43)*	564	430 (0.10)	134 (0.25)*
Cervix	180	2526	2213 (0.25)	313 (0.30)†				2526	2213 (0.50)	313 (0.57)†
Kidney	189	1556	1205 (0.14)	351 (0.34)*	837	660 (0.15)	177 (0.36)*	719	545 (0.12)	174 (0.32)*
Lymphoma	200-202	1912	1641 (0.19)	271 (0.26)*	888	746 (0.17)	142 (0.28)*	1024	895 (0.20)	129 (0.24)
Esophagus	150	1206	1028 (0.12)	178 (0.17)*	560	467 (0.11)	93 (0.19)*	646	561 (0.13)	85 (0.16)
Pancreas	157	798	543 (0.06)	255 (0.24)*	421	282 (0.06)	139 (0.28)*	377	261 (0.06)	116 (0.21)*
Bile duct	156	435	299 (0.03)	136 (0.13)*	233	153 (0.03)	80 (0.16)*	202	146 (0.03)	56 (0.10)*
Larynx	161	554	453 (0.05)	101 (0.10)*	422	341 (0.08)	81 (0.16)*	132	112 (0.03)	20 (0.04)
Ovary	183	1164	1034 (0.12)	130 (0.12)				1164	1034 (0.23)	130 (0.24)
Thyroid	193	1005	876 (0.10)	129 (0.12)†	216	177 (0.04)	39 (0.08)†	789	699 (0.16)	90 (0.17)
Leukemia	204-208	292	255 (0.03)	37 (0.04)	165	144 (0.03)	21 (0.04)	127	111 (0.03)	16 (0.03)
Uterus	179	301	252 (0.03)	49 (0.05)*				301	252 (0.06)	49 (0.09)†

DM indicates diabetes mellitus.

* $P < .001$ with DM vs without DM.

† $P < .005$ with DM vs without DM.

further confirmed by treatment at baseline prescribed by validated physicians that included 2 or more monthly packs of antihypertensives, antihyperlipidemia, and antigout or antihyperuricemic agents, respectively, in 1998.

2.4 Statistical methods

We performed 2 major statistical analyses in this study. First, the differences in demographic characteristics between patients with diabetes and cancer, including age, sex, hypertension, dyslipidemia, and gout, were analyzed using the χ^2 test. Second, to determine the independent effects of diabetes on the risks of any types of cancer, we used Cox proportional hazard regression models with age, sex, and possible associated risk factors adjusted simultaneously in the model. We adjusted age and sex for the incidence of any types of cancer. Furthermore, we explored the relative hazards of any types of cancer in relation to diabetes accompanied by the selected possible associated risk factors individually with Cox proportional hazard regression models with age, sex, hypertension, dyslipidemia, and gout adjusted in the model. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC). A P value < .05 was considered statistically significant.

3. Results

Of the 985 815 patients included in this study (488 778 males and 497 037 females), 104 343 diabetic patients (prevalence rate, 10.6%) were followed up from 1998 to 2009. Among them, 49 859 were male and 54 484 were female. The incidences of different types of cancer in the patients with and without diabetes mellitus are shown in Table 1. The most common forms of cancer in the diabetic patients were liver, colon, lung, breast, and prostate cancer, with incidences of 1.58%, 1.52%, 1.24%, 0.58%, and 0.62%, respectively. In male diabetic patients, the most common forms of cancer were liver, colon, lung, and prostate cancer, with incidences of 1.93%, 1.64%, 1.63%, and 1.30%, respectively; and in female diabetic patients, the most common forms of cancer were colon, liver, breast, and lung cancer, with incidences of 1.41%, 1.26%, 1.10%, and 0.87%, respectively. These incidences of the most common forms of cancer in diabetes, both in males and females, were all higher than those of nondiabetic patients.

The distribution of sex, age, and prevalence of hypertension, dyslipidemia, and gout in cancer subjects with and without diabetes is shown in Table 2. Female diabetic patients had a lower prevalence of any cancer than female nondiabetic patients (51.11% vs 53.45%). However, the prevalence rates of liver, colon, lung, and breast cancer in subjects with diabetes were higher than those in subjects without diabetes. In contrast, male diabetic patients had a higher prevalence of any cancer than nondiabetic patients (48.89% vs 46.55%), although they had lower prevalence rates of liver, colon, and lung cancer.

Prostate cancer had an equal prevalence of 100.0% in both diabetic and nondiabetic patients. The prevalence rates of cancer in diabetic patients older than 60 years were higher than the those of nondiabetic patients in any site and in the liver, colon, lung, breast, and prostate (86.23% vs 53.04%, 81.82% vs 52.11%, 87.42% vs 60.34%, 88.24% vs 73.51%, 79.07%

Table 2 – Distribution of sex, age, and prevalence of hypertension, dyslipidemia, and gout in cancer subjects with and without diabetes

	With DM						Without DM					
	With cancer (n = 632) n (%)	Liver (n = 121) n (%)	Colon (n = 159) n (%)	Lung (n = 102) n (%)	Breast (n = 43) n (%)	Prostate (n = 60) n (%)	With cancer (n = 34 309) n (%)	Liver (n = 5843) n (%)	Colon (n = 6543) n (%)	Lung (n = 4375) n (%)	Breast (n = 3949) n (%)	Prostate (n = 2170) n (%)
Sex												
Female (n = 497 037)	323 (51.11)	57 (47.11)	80 (50.31)	46 (45.10)	43 (100.00)	0	18 338 (53.45)	2313 (39.59)	3069 (46.90)	1654 (37.80)	3868 (97.95)	0
Male (n = 488 778)	309 (48.89)	64 (52.89)	79 (49.68)	56 (54.90)	0	60 (100.0)	15 971 (46.55)	3530 (60.41)	3474 (53.09)	2721 (62.19)	81 (2.05)	2170 (100.00)
Age (y)												
>60 (n = 162 405)	545 (86.23)	99 (81.82)	139 (87.42)	90 (88.24)	34 (79.07)	59 (98.33)	18 198 (53.04)	3045 (52.11)	3948 (60.34)	3216 (73.51)	1358 (34.39)	1915 (88.25)
50-59 (n = 140 188)	62 (9.81)	16 (13.22)	16 (10.06)	10 (9.80)	7 (16.28)	1 (1.67)	7493 (21.84)	1389 (23.77)	1232 (18.83)	666 (15.22)	1394 (35.30)	180 (8.29)
40-49 (n = 165 171)	21 (3.32)	4 (3.30)	2 (1.26)	2 (1.96)	2 (4.65)	0	5003 (14.58)	935 (16.00)	773 (11.81)	332 (7.6)	881 (22.31)	44 (2.03)
30-39 (n = 171 112)	4 (0.63)	2 (1.65)	2 (1.26)	0	0	0	2410 (7.02)	380 (6.50)	452 (6.91)	108 (2.5)	242 (6.13)	27 (1.24)
<30 (n = 347 506)	0	0	0	0	0	0	1205 (3.51)	94 (1.61)	138 (2.11)	53. (1.2)	74 (1.87)	4 (0.18)
Hypertension (n = 168 399)	521 (82.44)	95 (78.51)	129 (81.13)	88 (86.27)	35 (81.39)	50 (83.33)	15 322 (44.66)	2589 (44.31)	3237 (49.47)	2485 (56.8)	1286 (32.56)	1407 (64.84)
Dyslipidemia (n = 154 349)	434 (68.67)	65 (53.72)	117 (73.58)	71 (69.61)	32 (74.42)	48 (80.00)	11 861 (34.57)	2146 (36.73)	2628 (40.16)	1632 (37.3)	1259 (31.88)	926 (42.67)
Gout (n = 74 651)	165 (26.11)	23 (19.01)	54 (33.96)	33 (32.35)	8 (18.60)	16 (26.67)	5475 (15.96)	1051 (17.99)	1182 (18.06)	849 (19.4)	386 (9.77)	597 (27.51)

All factors showed a significant association with DM.

Table 3 – Unadjusted and adjusted risk ratios for the 5 most common cancer sites and any site in diabetic patients

Cancer site	Unadjusted RR (95% CI)	*P* value	Adjusted RR (95% CI)	*P* value
Any cancer site	4.7 (4.28-5.08)	<.001	1.56 (1.43-1.71)	<.001
Liver	4.75 (3.96-5.7)	<.001	1.67 (1.39-2.01)	<.001
Colon	5.62 (4.79-6.59)	<.001	1.75 (1.49-2.06)	<.001
Lung	5.32 (4.37-6.49)	<.001	1.54 (1.26-1.88)	<.001
Breast (female)	2.24 (1.65-3.03)	<.001	1.01 (0.74-1.37)	.9614
Prostate	6.97 (5.34-9.10)	<.001	1.56 (1.19-2.04)	.0013

Adjusted risk ratio: adjusted for age, sex, history of hypertension, dyslipidemia, and gout. RR indicates risk ratio.

vs 34.39%, and 98.33% vs 88.25%, respectively). However, these percentages were far lower with a secular trend in the 50- to 59-, 40- to 49-, 30- to 39-, and less-than-30-years-old age groups of diabetic patients than those in nondiabetic patients in any site and in liver, colon, lung, breast, and prostate cancer. The prevalence rates of hypertension, dyslipidemia, and gout were higher in diabetic patients with cancer than in nondiabetic patients with cancer, except for gout in prostate cancer, which was slightly lower in diabetic than in nondiabetic patients (26.67% vs 27.51%).

Table 3 shows an increased incidence of cancer in patients with diabetes, with a risk ratio of 4.7 (95% confidence interval [CI], 4.28-5.08). Liver, colon, lung, breast, and prostate cancer had the highest incidences of cancer in diabetes mellitus, with risk ratios of 4.75 (95% CI, 3.96-5.7), 5.62 (95% CI, 4.79-6.59), 5.32 (95% CI, 4.37-6.49), 2.24 (95% CI, 1.65-3.03), and 6.97 (95% CI, 5.34-9.10), respectively ($P < .001$). After adjusting for sex, age, hypertension, dyslipidemia, and gout, there was still an increased incidence of cancer in diabetes mellitus, with a risk ratio of 1.56 (95% CI, 1.43-1.71); and the risk ratios were 1.67 (95% CI 1.39-2.01), 1.75 (95% CI 1.49-2.06), 1.54 (95% CI 1.26-1.88) and 1.56 (95% CI 1.19-2.04) in liver, colon, lung, and prostate cancer, respectively. After adjusting for sex, age, hypertension, dyslipidemia, and gout, there was no clinical significance with breast cancer.

4. Discussion

The most important finding in this study is that the incidences of the most common cancers, such as liver, colon, lung, and prostate cancer, but not breast cancer, increased independently in diabetic patients with hypertension, dyslipidemia, and gout. Although some experts suggest that an increased cancer incidence in diabetes may be related to its disease complexity with a group of metabolic and hormonal derangements characterized by hyperglycemia, obesity, hypertension, dyslipidemia, and gout; to nonmodifiable risk factors (eg, age, sex, race or ethnicity); and to modifiable risk factors (ie, diet, physical activity, tobacco smoking, alcohol, and metabolic syndrome) [2], the current study shows that an increased incidence of cancer in diabetes may be independent of hypertension, dyslipidemia, and gout.

An estimated 285 million people between 20 and 79 years of age have diabetes worldwide, with a prevalence rate of 6.6% [4], including 8% of the population aged 19 years and older in Taiwan in 2009 [5]. In the study population, there was a diabetes prevalence rate of 10.6% in 1998. In 2007, cancer was the second and diabetes the 12th leading causes of death worldwide [6]. In Taiwan, cancer was the first and diabetes the fifth leading cause of death in 2009 [5]. The most commonly diagnosed cancers are lung, breast, and colorectal cancer, whereas the most common causes of cancer deaths are lung, stomach, and liver cancer [7].

Even after adjusting for age and sex, diabetes and cancer coexist frequently, especially in type 2 diabetes mellitus. Several meta-analytic studies have shown that liver, pancreatic, and endometrial cancers have a 2-fold or higher risk in diabetic patients, whereas colorectal, breast, and bladder cancers have a 1.2- to 1.5-fold higher risk. Diabetes is associated with a reduced risk of prostate cancer and is not associated with lung cancer [1]. In this study, there was a 4.7-fold increased risk of cancer with diabetes. Specifically in liver, colon, lung, breast, and prostate cancer, there were increases of 4.75-, 5.62-, 5.32-, 2.24-, and 6.97-fold in diabetes, respectively.

Liver cancer is the most common cancer in insulin-resistant hyperinsulinemic type 2 diabetes mellitus, but not in type 1 diabetes mellitus treated with exogenous insulin [8]. In this study, there was an increased risk of liver cancer of up to 4.75-fold in diabetes compared with 2- to 3-fold in other studies [9]. The liver is exposed to endogenous insulin in high concentrations more frequently than other tissues because of insulin transported via the portal vein. Other diabetes-related diseases such as hepatitis B and C infections, steatosis, nonalcoholic fatty liver disease, and cirrhosis are all well-known risk factors increasing the susceptibility to liver cancer [10,11]. Liver inflammation and hepatocyte damage and repair are possible mechanisms, but the exact mechanism is still unclear.

In this study, colon cancer was also a common cancer in diabetes, with a 5.62-fold higher risk ratio compared with other studies [12,13]. The hyperinsulinemic state of diabetes, slower bowel transit time, and elevated fecal bile acid concentrations frequently observed in diabetes are the possible mechanisms [14,15].

Lung cancer had an increased risk of 5.32-fold in the study population. However, lung cancer does not appear to have an increased risk in diabetes in other studies and even has a reduced risk in thiazolidinedione users [16]. This difference may be due to the factor of glucose-lowering agents taken by diabetic patients that may complicate the situation.

An inverse association of diabetes with prostatic cancer has been noted in several studies, which may be due to reduced testosterone levels in diabetes, altered insulin and leptin concentrations, statins and metformin use, and changes in

diet and lifestyle in controlling diabetes [17-19]. However, there was a 6.97-fold increased risk of prostate cancer in this study, which may be due to the lack of associated protective factors mentioned in the other studies [17-19].

The incidence of breast cancer has also been shown to increase in diabetes, both in this and other studies. In this study, there was an increased risk of 2.24-fold; other studies reported increased risk of 1.1- to 1.2-fold [20]. Several biological mechanisms such as sex hormone abnormalities and hyperinsulinemia increase the levels of bioactive estrogens by decreasing the concentration of circulating sex hormone-binding globulins. This may also stimulate androgen synthesis in the ovarian stroma [21].

The potential nonmodifiable risk factors common to both cancer and diabetes are aging and sex. Although the incidence of some types of cancer peaks in childhood or adolescence, the risk of most cancers increases with age. In this study, diabetic patients older than 60 years had a higher risk for any cancer than nondiabetic patients of the same age, whereas nondiabetic patients younger than 60 years had a higher incidence of cancer than age-matched diabetic patients. This suggests that the duration of diabetes may also be a possible mechanism due to tissue exposure to hyperinsulinemia for a longer time leading to cancer. Breast and prostate cancers are specific to sex. Overall, cancers are more common in male diabetic patients [22] both in this and in other studies. In liver, colon, and breast cancers, female diabetic patients are at a higher risk than female nondiabetic patients. In prostate cancer, there is an equal incidence between male diabetic and nondiabetic patients.

Other modifiable risk factors that can influence the risk of cancer in diabetes are obesity, physical activity, diet, alcohol, and smoking [2]. Other metabolic diseases commonly coexisting with diabetes, such as metabolic syndrome, hypertension, dyslipidemia, and gout, are also expected to be contributing risk factors for cancer in diabetes by some experts. In this study, the frequencies of hypertension, dyslipidemia, and gout were higher in cancer subjects with diabetes than in cancer subjects without diabetes. This suggests that hypertension, dyslipidemia, and gout may also be associated with an increased risk of cancer in diabetes.

Both hypertension and diabetes are chronic degenerative diseases that accelerate the biological process of aging that favors carcinogenesis. The metabolic derangements of hypertension and diabetes increase oxidative stress and cause a permanent proinflammatory state that reduces intracellular antioxidant capacity and predisposes to malignant transformation [23]. Reactive oxygen species generated by diverse free radicals and oxidants can cause cell deoxyribonucleic acid (DNA) damage by direct oxidation or by interfering with cell DNA repair. Reactive oxygen species can also form derivatives and alter intracellular homeostasis by reacting with proteins and lipids favoring the accumulation of mutations [24]. Another mechanism may be due to mitochondrial dysfunction, which, perhaps because of increased DNA repair activity, provides a low, insufficient energy supply that increases reactive oxygen species production [25]. Tumor necrosis factor (TNF)–α as a proinflammatory cytokine may also play a role in inducing the development and progression of many tumors by strongly activating nuclear factor–κB [26,27].

In dyslipidemia and diabetes, fatty acid synthase (FASN) activity and fatty acid production are also considered as possible mechanisms of an increased cancer risk in diabetes. Fatty acid synthase is important in de novo fatty acid synthesis in the liver and is stimulated by a low-fat/high-carbohydrate diet, which can also be involved in the pathogenesis of insulin resistance, diabetes, and cancer [28]. There was an increase in liver cancer in this study, which can be explained by increased FASN activity and worsened insulin resistance, resulting in nonalcoholic fatty liver disease and an increased risk of hepatocarcinoma.

Increased FASN activity is also present in cancer cells, where de novo fatty acid synthesis is crucial for membrane remodeling during cell migration and proliferation, as well as for lipid-based posttranslational modifications of intracellular proteins in highly proliferating populations [29]. Fatty acid synthase is also involved in affecting tumor progression by cell exposure to FASN blocker cerulenin, resulting in cytostatic, cytotoxic, and apoptotic effects in vitro [30].

Hyperuricemia may be an early manifestation of the carcinogenic process. Gout patients might be at an increased risk of oral cavity and pharynx, colon, liver and biliary tract, pancreas, lung, skin (melanoma and nonmelanoma), endometrium, and kidney cancer, as well as malignant melanoma, because of obesity and heavy alcohol drinking, with the exception of lung cancer [31,32], contrary to some previous studies that showed that uric acid has antioxidant properties, which may protect against carcinogenesis [33,34].Gout is a disease that is manifested by an increase in serum urate concentration, recurrent attacks of acute arthritis, and deposits of monosodium urate monohydrate in and around the joints of the extremities. Monosodium urate monohydrate crystals have been shown to stimulate synovial cells, monocytes-macrophages, and neutrophils to produce a variety of cytokines, including TNF-α, interleukin (IL)-8, IL-1β, IL-6, and monocyte chemotactic factor, which induce acute inflammation [35]. Among them, TNF-α, IL-8, IL-1β, and IL-6 are produced by activated macrophages. Each of these factors may play an etiologic role in regulating the malignant transformation or cancer progression. In some cases, the roles of these molecules are well known. Activation of signal transducer and activator of transcription protein signaling, via cytokines such as IL-6, is known to enhance cancer cell proliferation, survival, and invasion, while also suppressing host antitumor immunity [36].

In this study, breast cancer was the only cancer that did not increase in diabetes in the presence of hypertension, dyslipidemia, and gout. However, some inflammatory cytokines such as the plasminogen system have been linked with cancer via the expression of plasminogen activator inhibitor–1, which is linked to poor outcomes in breast cancer.

There were several methodological strengths and limitations in our study. First of all, our study has a prospective design, long follow-up, and very large cohort of diabetic and cancer patients. There is a probable completeness of ascertainment of diagnosis in cancer and diabetes by obtaining the computerized data file for each individual from the National

Health Insurance Research Database, which is population-based and highly representative, causing little possibility of recall and selection bias. In addition, there is little likelihood of nonresponse and loss to follow-up of cohort members. Nevertheless, there are some limitations. There may be increased detection bias in the diabetic patients because of frequent visits to their physicians, rendering a higher probability of detecting the existence of cancers. However, this may only suggest a higher detection rate of early and slower progressive cancer with better prognosis in diabetic patients. Diabetic patients may have taken more medications than those without diabetes, which may have complicated the situation. This study did not evaluate the effects of medications; and data for established risk factors for the cancers examined like duration and treatment regimens of diabetes, smoking, alcohol consumption, other socioeconomic characteristics in our study population, and major modifiable determinants of diabetes and insulin resistance, such as obesity, were not reviewed because of a lack of data on body mass index, which might have also confounded the study results. However, assuming that most patients with type 2 diabetes mellitus are overweight or obese, we can assume that this factor has been considered. Given the lack of control for known risk factors for cancer as well as gout, the respective data here should be interpreted with caution. Furthermore, because we only selected those patients with major illness/injury certificates/catastrophic illness cards for the accuracy of diagnosis of cancer, we might have missed some patients who had been waiting for the pathological diagnosis and had not received major illness/injury certificates/catastrophic cards. Such misclassification bias, however, was likely to be nondifferential, which tends to underestimate rather than overestimate the true relative risks.

Most epidemiologic studies have considered a series of confounding factors such as the metabolic syndrome and classified hypertension, dyslipidemia, and gout, which commonly coexist with diabetes, as risk contributing factors for cancer in diabetes. However, in the current study, the common comorbidities of diabetes were independently associated with cancer. Although their role as risk factors for cancer development may be independent of diabetes, their increased effect on cardiovascular risk still warrants public health attention. Furthermore, the risk of cancer was increased in diabetic patients. Because the population is aging and the incidence of diabetes is increasing, patients with diabetes should be strongly encouraged by physicians to undergo appropriate cancer screenings as recommended for their age and sex.

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Conflict of Interest

There are no potential conflicts of interest with any author involved in this manuscript.

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