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A Retrospective Study On Diabetes Mellitus, Metformin, And Head And Neck Cancer.

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ABSTRACT

Background-More research was needed to determine whether metformin use could impact the risk of oral cancer.
Methods: During 2015-
2025, patients with type 2 diabetes mellitus who had recently started taking metformin (n = 288198, “ever users of metfor min”) or other antidiabetic medications (n = 16263, “never users of metformin”) were monitored for oral cancer for at lea st six months until December 31, 2011.Cox regression adjusted for propensity score (PS) or integrated with the inverse pr obability of treatment weighting (IPTW) using PS was used to evaluate the treatment impact of metformin (forever versus never users, and for tertiles of cumulative length of therapy). **Results-** There were also 1273 (0.44%) and 119 (0.73%) occurrence cases of cancer of the mouth among ever users and never users, respectively, with rates of 92.7 and 163.6 per 100,000 person-years. A substantially decreased risk was indicated by the overall hazard ratios (95% CIs) [0.584 (0.483-0.707) for the PS-added model and 0.562 (0.465-0.678) for the IPTW approach]. The PS-adjusted hazard ratios (95% confidence intervals) for the first (<21.5 months), second (21.5-45.9 months), and third (>45.9 a period of time tertiles of cumulative time span were 1.403 (1.152-1.708), 0.557 (0.453-0.684), and 0.152 (0.119-0.194) for IPTW. **Conclusions**- The possibility of developing oral cancer may be considerably decreased by metformin, particularly if the cumulative period exceeds 21.5 months.

Keywords: oral cancer, diabetes mellitus, metformin..

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1. INTRODUCTION

The breast, endometrium, colon, thyroid, oesophagus, pancreas, stomach, and prostate are among the cancer cell types in which metformin has anticancer effects. Additionally, metformin treatment may lower the risk of colon, bladder, breast, prostate, thyroid, endometrial, and ovarian cancers in persons with type 2 diabetes mellitus, according to epidemiological research. It is yet unknown, nevertheless, if taking metformin can lower the risk of oral cancer in diabetic patients.1,2

Metformin may prevent human head and neck squamous cell carcinoma from growing in cancer cell lines, according to some recent research. Epidemiological research assessing metformin's impact on oral cancer is relatively uncommon, nevertheless. A recent meta-analysis 3 indicated that there are only three studies available from the literature: one from Taiwan comparing the incidence of head and neck cancer in patients with diabetes who used and did not use metformin, and two from the USA assessing the impact of metformin on the survival of patients with head and neck cancer. 4,5 Individuals with diabetes who took metformin had a 34% decreased chance of developing head and neck cancer (adjusted hazard ratio 0.66, 95% CI 0.55-0.79), and users also had a higher life expectancy rate for those who developed cancer of the head and throat.

Nevertheless, the lower incidence of oral cancer among metformin users was not statistically significant in the Indore trial when head and neck cancer was divided into multiple groups. The 95% confidence interval for the adjusted hazard ratio was 0.81 (0.63-1.03).

Methodology

Individuals with type 2 diabetes mellitus who had been newly treated with metformin (n = 288198, "ever users of metformin") or different antidiabetic medications (n = 16263, "never users of metformin") and who had onset age between 25 and 74 years in 2015–2025 were monitored for oral cancer for at least six months until December 31, 2025. Cox regression adjusted for propensity score (PS) or integrated with the inverse probability of treatment weighting (IPTW) using PS was used to evaluate the treatment impact of metformin (for ever versus never users, and for tertiles of cumulative length of therapy).

To ensure secrecy, personal identifiable information was jumbled.
The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-
CM) was used to categorise diabetes 250.XX and oral cancer 140, 141, 143, 144, 145, 146, 148, and 149.
Additionally, incident metformin users and newly diagnosed diabetic patients were enlisted to address the possible issue of "prevalent user bias."
Participants comprised of the research will have been prescribed antidiabetic medications at least twice in order to minim ise the risk of "immortal time bias," which is the first phase of examination through which the outcome is unlikely to occur. Assessments did not include patients who were monitored for fewer than 180 days. Cox regression models either were corrected for the standard propensity score (PS) or integrated with the inverse probability model of treatment weighting (IPTW) using PS in order to prevent possibility of confusion from the variations in baseline characteristics linked to treatment allocation in non-random observations. To assess the coherence of the results, analyses were performed on both an original sample taken from the NHI database and a matched-pair sample taken from an initial collection.

Results

The first sample consisted of 288198 ever users and 16263 never users (Figure 1). With the exception of pioglitazone, every baseline parameter (determined at the beginning of follow-up) between the two categories in the original cohort varied appreciably. Younger ages, fewer males, higher rates of eye disease, dyslipidaemia, vascular disease, and tobacco product abuse, reduced incidences of hypertension, nephropathy, stroke, ischaemic heart disease, chronic obstructive pulmonary disease, and alcohol-related health conditions, more prevalent rates of rosiglitazone, statins, and non-steroidal anti-inflammatory drugs (apart from aspirin), but low rates of other antidiabetic medication, angiotensin converted enzyme inhibitors, and aspirin receptor blockers.

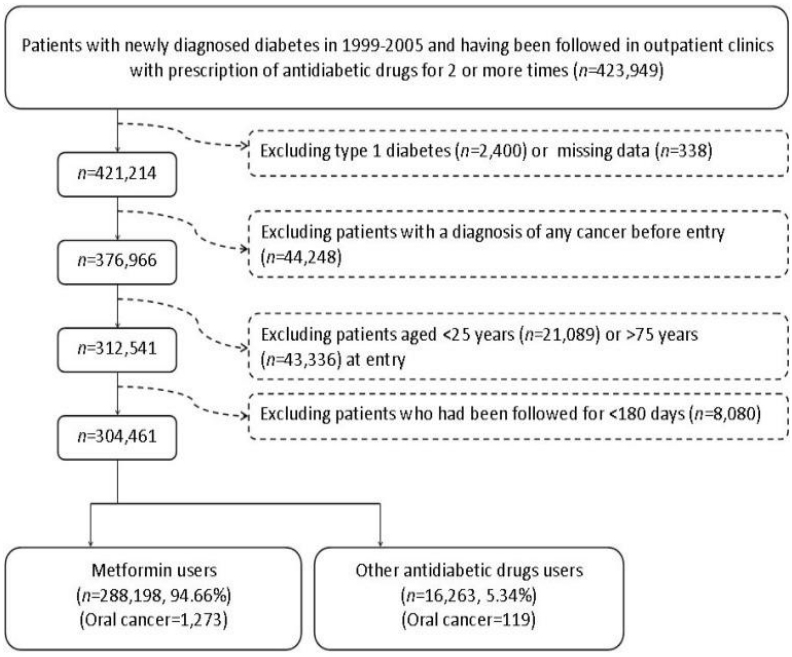

Figure 1. Flowchart showing the procedure in selecting the original sample into the study.

Table 1. Comparison of baseline characteristics between metformin never users and ever users in the original sample and in the propensity score matched sample.

Variable	Original sample						Matched sample					
	Never users (n = 16263)		Ever users (n = 288198)		*P*	SD	Never users (n = 16263)		Ever users (n = 16263)		*P*	SD
	n	%	n	%			n	%	n	%		
Demographic data												
Age (years)	59.1±10.4		56.6±10.2		<0.0001	−25.14	59.1±10.4		59.4±9.7		0.0197	3.54
Sex (men)	9332	57.4	155199	53.9	<0.0001	−7.31	9332	57.4	9437	58.0	0.2386	0.98
Major comorbidities												
Hypertension	11995	73.8	198483	68.9	<0.0001	−11.31	11995	73.8	12033	74.0	0.6315	0.98
Dyslipidemia	9855	60.6	197488	68.5	<0.0001	17.23	9855	60.6	9690	59.6	0.0617	−1.56
Diabetes-related complications												
Nephropathy	4139	25.5	46223	16.0	<0.0001	−25.22	4139	25.5	4123	25.4	0.8385	−1.01
Eye disease	1529	9.4	41653	14.5	<0.0001	15.66	1529	9.4	1341	8.3	0.0002	−4.72
Stroke	4021	24.7	54814	19.0	<0.0001	−14.73	4021	24.7	3947	24.3	0.3401	−0.90
IHD	6218	38.2	98033	34.0	<0.0001	−9.33	6218	38.2	6256	38.5	0.6648	0.67
PAD	2516	15.5	45915	15.9	<0.0001	1.20	2516	15.5	2505	15.4	0.8659	−0.32
Antidiabetic drugs												
Sulfonylurea	11832	72.8	189914	65.9	<0.0001	−11.51	11832	72.8	12560	77.2	<0.0001	11.65
Meglitinide	1338	8.2	10353	3.6	<0.0001	−20.99	1338	8.2	1245	7.7	0.0565	−1.87
Acarbose	1835	11.3	14531	5.0	<0.0001	−22.46	1835	11.3	1718	10.6	0.0376	−4.03
Insulin	1351	8.3	6100	2.1	<0.0001	−29.42	1351	8.3	990	6.1	<0.0001	−10.71
Pioglitazone	403	2.5	7024	2.4	0.7428	0.31	403	2.5	435	2.7	0.2627	0.51
Rosiglitazone	483	3.0	12961	4.5	<0.0001	8.43	483	3.0	441	2.7	0.1610	−1.98
Potential risk factors of oral cancer												
COPD	6521	40.1	110809	38.5	<0.0001	−3.84	6521	40.1	6599	40.6	0.3780	1.19

Tobacco abuse	266	1.6	5915	2.1	0.0002	3.19	266	1.6	247	1.5	0.3978	−0.89
Alcohol-related diagnoses	1037	6.4	15451	5.4	<0.0001	−4.77	1037	6.4	1059	6.5	0.6193	0.21
Medications that may affect cancer risk												
ACEI/ARB	9609	59.1	163730	56.8	<0.0001	−5.07	9609	59.1	9660	59.4	0.5650	0.74
Statin	6438	39.6	127216	44.1	<0.0001	9.44	6438	39.6	6354	39.1	0.3403	−0.82
Aspirin	7672	47.2	133390	46.3	0.0267	−2.16	7672	47.2	7560	46.5	0.2133	−1.04
NSAID	16180	99.5	287188	99.7	0.0009	2.70	16180	99.5	16186	99.5	0.6344	0.90

Table 2. Incidences of oral cancer by metformin exposure in the original sample and the hazard ratios comparing metformin exposed to unexposed patients in the original sample and the matched sample.

Original sample								Matched sample				
Metformin use	*n/N*	Person-years	Incidence rate(per 100,000 person-years)	PS-adjusted model		IPTW model		*n/N*	PS-adjusted model		IPTW model	
				HR (95% CI)	*P*	HR (95% CI)	*P*		HR (95% CI)	*P*	HR (95% CI)	*P*
Never users	119/16263	72760.7	163.6	1.000		1.000		119/16263	1.000		1.000	
Ever users	1273/288198	1373325.0	92.7	0.584 (0.483-0.707)	<0.0001	0.562 (0.465-0.678)	<0.001	77/16263	0.592 (0.444-0.789)	0.003	0.602 (0.452-0.802)	0.00005
Tertiles of cumulative duration of metformin therapy (months)												
Never users	119/16263	72760.7	163.6	1.000		1.000		119/16263	1.000		1.000	
<21.5	715/95463	344951.9	207.3	1.403 (1.152-1.708)	0.0008	1.244 (1.024-1.511)	0.0281	35/5287	1.176 (0.806-1.717)	0.4000	1.127 (0.772-1.645)	0.5359
21.5-45.9	418/94666	471050.1	88.7	0.557 (0.453-0.684)	<0.0001	0.526 (0.429-0.645)	<0.001	31/5307	0.693 (0.466-1.029)	0.0689	0.703 (0.473-1.043)	0.0802
>45.9	140/98069	557322.9	25.1	0.152 (0.119-0.194)	<0.0001	0.138 (0.108-0.176)	<0.001	11/5669	0.197 (0.106-0.366)	<0.0001	0.205 (0.110-0.380)	<0.0001

n*: incident cases of oral cancer, N: cases followed, HR: hazard ratio, CI: confidence intervals*

PS: propensity score created from variables in Table 1
IPTW: Cox regression model incorporated with the inverse probability of treatment weighting (IPTW) using PS

Table 3. Hazard ratios for oral cancer in different subgroups of metformin exposure with or without other antidiabetic drugs in comparison to a referent group who had never used metformin in the original sample

Different subgroups of metformin use	*n* / *N*	PS-adjusted model			IPTW model		
		HR	95% CI	*P*	HR	95% CI	*P*
Classification I							
Never users	119 / 16263	1.000			1.000		
Metformin only	265 / 79327	0.486	(0.391-0.603)	<0.0001	0.466	(0.376-0.579)	<0.0001
Metformin as the first OAD with add-on of other OADs, but without insulin	418 / 83933	0.631	(0.514-0.775)	<0.0001	0.594	(0.485-0.728)	<0.0001
Metformin as add-on to other OADs, but without insulin	565 / 118838	0.624	(0.512-0.762)	<0.0001	0.594	(0.487-0.724)	<0.0001
Metformin with insulin (with or without other OADs)	25 / 6100	0.617	(0.400-0.951)	0.0286	0.571	(0.371-0.878)	0.0108
Classification II							
Never users	119 / 16263	1.000			1.000		
Metformin only	265 / 79327	0.486	(0.391-0.603)	<0.0001	0.466	(0.376-0.579)	<0.0001
Metformin as the first OAD with add-on of other OADs and/or insulin	430 / 86458	0.633	(0.515-0.777)	<0.0001	0.595	(0.486-0.729)	<0.0001
Metformin as add-on to other OADs and/or insulin	578 / 122413	0.623	(0.510-0.760)	<0.0001	0.592	(0.486-0.721)	<0.0001

n: incident cases of oral cancer, N: cases followed, HR: hazard ratio, CI: confidence intervals, OAD: oral antidiabetic drug

PS: propensity score created from variables in Table 1

IPTW: Cox regression model incorporated with the inverse probability of treatment weighting (IPTW) using PS

Discussion

According to the results of this observational investigation, persons with type 2 diabetes mellitus who take metformin had a much lower chance of developing oral cancer. This was seen in the second and third tertiles of cumulative duration of metformin medication as well as in the overall analysis comparing ever users versus never users (Table 2).

The potential advantage of metformin in combination with other chemotherapy regimens for certain solid malignancies, such as lung, breast, endometrial, and prostate cancer, is being assessed in a number of randomised clinical trials.[6] Nevertheless, there are currently no clinical trials that specifically examine the impact of metfomin on oral cancer. The present study offered a crucial hint for a thorough examination of metformin's effects on oral preventing and curing cancer.

Metformin-using diabetic patients had a substantially decreased incidence of head and neck cancer (34%) in the earlier study by Yen et al.[4] Nevertheless, if certain types of site-specific head and neck cancer were examined, they did not find a significantly lower incidence of oral cancer linked to metformin use.[4] The adjusting danger ratio of 0.81 (95% confidence interval: 0.63-1.03) indicated a decreased incidence of oral cancer in metformin users even if it was not statistically significant. The Yen et al. study's lack of statistical significance could be explained by a few factors.[4] First, the sample sizes of metformin users and cases of oral cancer were much smaller in this previous study and this could lead to a lack of statistical power. Second, as noted in the present study, the risk of oral cancer was actually increased in the first tertile of cumulative duration of metformin therapy of less than 21.5 months in the original sample (Table 2). If the previous study included more metformin users with a short duration of use and did not consider the potential imbalance in baseline characteristics between metformin users and non-users, the estimated hazard ratio might be substantially biased toward the null. Third, the lack of investigating a dose-response relationship might have concealed much of the information in the previous study

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