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Metformin exposure and survival in head and neck cancer: A large population-based cohort study

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Summary

What is known and objective: Observational clinical studies of metformin for prevention and treatment of several cancer types have reported mixed findings. Although preclinical studies have suggested metformin may reduce head and neck cancer (HNC) proliferation, clinical evidence is limited. The objective of this large population-based study was to evaluate the relationship between metformin exposure following HNC diagnosis and all-cause mortality.

Methods: We conducted a retrospective cohort study using the Italian Emilia-Romagna Regional administrative healthcare database, which includes demographic, hospital and outpatient prescription information for ~4.5 million residents. Included patients were followed from the first hospital discharge (index) during the study period (01/2003-12/2012) with a diagnosis of HNC. Metformin exposure and select covariates were operationalized in a time-dependent manner during follow-up. Cox proportional hazards models estimated the covariate-adjusted time-dependent association between metformin exposure and all-cause mortality.

Results and discussion: Among 7872 patients diagnosed with HNC, 708 (9.0%) were exposed to metformin after HNC diagnosis, and 3626 (46.1%) died during follow-up (median follow-up: 35.2 months). In the covariate-adjusted model, the all-cause mortality rate appeared lower (HR: 0.81, 95% CI: 0.61-1.09) among metformin exposed patients during the 2 years post-diagnosis, while the all-cause mortality rate appeared higher (HR: 1.20, 95% CI: 0.94-1.53) among exposed patients after 2 years post-diagnosis. Metformin was protective among patients ≤60 years of age (HR for the period of 0-2 years post-diagnosis: 0.22, 95% CI 0.09-0.56; HR for the period ≥2 years post-diagnosis: 0.56, 95% CI 0.26-1.22) but not in those >60 years.

What is new and conclusion: In this population-based study of metformin in HNC, we found a modest protective association between metformin exposure and all-cause mortality in the 2-year post-diagnosis period. Age appeared to modify the association between metformin and HNC survival.

KEYWORDS
pharmacoepidemiology, population analysis

1 | WHAT IS KNOWN AND OBJECTIVE

Head and neck cancer (HNC) refers to a group of malignancies that arise from the epithelial lining of the oral cavity, pharynx, larynx, nasal cavity or paranasal sinuses.[1] The number of HNC cases is increasing in the United States.[2] Incidence rates for HNC vary worldwide due to differences in exposure to risk factors, primarily smoking, although incidence is rising in young non-smokers due to human papilloma virus (HPV) infection.[3,4] Mortality in HNC is dependent upon site of disease, staging, perineural invasion, extracapsular spread and HPV status.[5-7] Despite new therapies and improved risk stratification, overall survival in subjects with advanced HNC remains poor and only 50%-60% of patients diagnosed with HNC are alive at 5 years.[7-9]

In in vitro and animal studies, the diabetes medication metformin has been shown to have beneficial effects on cancer development via multiple pathways.[10-12] In HNC, metformin has been documented to inhibit cell proliferation through induction of cell cycle arrest, activation of the adenosine monophosphate kinase pathway and deactivation of the mammalian target of rapamycin.[13-15] Observational studies have reported positive findings regarding preventative and treatment effects of metformin compared with other diabetes medications in other cancer types, yet many early comparisons were criticized for methodological issues due to immortal time and disease severity related biases.[16] Subsequent studies which have used time-varying exposure definitions to mitigate immortal time biases have continued to use other diabetes medication users as the comparison group.[17-21] Metformin's status as the first-line diabetes treatment option makes comparisons to second-line agents susceptible to confounding by indication, whereby patients in the comparison group have a longer history of diabetes and more advanced disease. Longer duration of diabetes is associated with increased risk of macrovascular complications and all-cause mortality,[22] a potential source of bias in favour of metformin. Use of a comparison group of all HNC patients may also be susceptible to confounding by indication. However, comparisons between metformin treated patients and a group of HNC patients largely without diabetes are expected to be more conservative in that bias introduced into the effect estimate will be against the metformin exposed group.

The few clinical studies that have evaluated the relationship between metformin exposure and health outcomes in patients with HNC were small single-centre studies[24,25]; one larger study reported a survival benefit of metformin but was subject to immortal time bias.[23] Motivated by positive preclinical data in HNC and evolving evidence of metformin's potential effects in oncology, our objective was to investigate the relationship between metformin exposure and survival after a diagnosis of HNC in a large population-based cohort.

2 | METHODS

The Regione Emilia-Romagna administrative healthcare database for the period of 1 January 2002 through 31 December 2012 was used for the present study. The database is composed of linkable de-identified demographic, hospital, all-cause mortality and outpatient pharmacy data on individual prescriptions, and has been used extensively for the purposes of pharmacoepidemiologic research.[26,27]

Patients discharged with at least one primary or secondary ICD-9 Clinical Modification (CM) diagnosis code (Online Appendix S1) for HNC cancer between 1 January 2003 and 31 December 2011 were identified as cases. The index date was defined as the date of discharge from the first hospital record containing a code for HNC. Patients included in the study were 18 years and older and resided in the Regione Emilia-Romagna for the entire year prior to the index date and for the entire index year. Patients with ≥1 ICD-9 CM code on or before the index date for a cancer of the tongue or other unspecified oral cavity cancer (V10.01, V10.02) were excluded. Cases were followed until death, movement out of the Regione Emilia-Romagna, or the end of the study follow-up period, 31 December 2012.

Regional involvement and metastases were identified in a time-dependent fashion using ICD-9 CM codes (Online Appendix S2) from hospital records on or after the date of diagnosis. Surgical resection, radiotherapy and chemotherapy administration were each identified from hospital records on or after the date of diagnosis as time-dependent covariates using ICD-9 CM diagnosis and procedural codes (Online Appendices S3, S4, and S5 respectively). Due to variability in pathophysiology and survival, specific HNC subtypes including oropharyngeal squamous cell carcinoma (OPSCC) and cancer of the larynx were each identified separately from other subtypes (Online Appendix S6).

Exposures to metformin and other medications/classes potentially impacting cancer progression including aspirin, beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), insulin and other diabetes medications (sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, meglitinides and incretin mimetics) were recorded dichotomously (ie, none vs any exposure) during the year prior to the index date. These medications were tracked as time-dependent covariates in the post-index period (Online Appendix S7). This time-dependent approach to exposure classification avoided the introduction of immortal time bias. Exposure was classified by quarter, for each quarter of survival time after diagnosis. Once a patient incurred exposure to a medication class after the index diagnosis, the patient remained classified as exposed for the remainder of the follow-up period. Exposure was lagged by one quarter, whereby exposure in a given quarter is reflected beginning in the subsequent quarter. Drug exposure was lagged to reflect an expected latency period between drug exposure and onset of an effect (ie, metformin is not expected to act immediately to prevent imminent death in an end-stage patient). Once a drug exposure occurred post-index, the remainder of the patient's follow-up was classified as exposed to that medication to facilitate detection of any effect on survival.

Descriptive statistics including medians with first and third quartiles were computed to summarize the distributions of

continuous variables, while frequencies and percentages were compiled for categorical variables. A Cox proportional hazards model was constructed to adjust for demographic and clinical variables and evaluate the association between metformin exposure after diagnosis of HNC and all-cause mortality. Initially, the metformin exposure-survival association was modelled over the entirety of the follow-up period. Upon checking the model for proportional hazards with graphical methods including log-log survival and hazard ratio plots, variability was observed in the metformin hazard ratio over time. A change in the hazard ratio from less than to greater than one was observed at approximately 2 years post-diagnosis, and a model was fit to evaluate a time-dependent association using this statistically significant threshold (interaction $P = 0.003$).

The following covariates were included in the model: exposure to metformin, aspirin, beta-blockers, NSAIDs, statins, ACE inhibitors or ARBs, and other diabetes medications, respectively, in the year prior to diagnosis; another set of post-index indicator covariates for the latter six drug exposures listed; indicator variables for OPSCC and cancer of the larynx; sex; age (and age^2); geographic location of residence (ie, rurality); mean-centred calendar time in years; time-dependent exposure to chemotherapy indicator; time-dependent exposure to radiation therapy indicator; time-dependent tumour resection indicator; time-dependent diagnosis of regional and metastatic disease indicator; and Elixhauser comorbidity score (modified to omit diabetes and cancer diagnoses).[28] Diabetes was not included as a covariate because all metformin users were expected to have diabetes (or prediabetes). However, use of other diabetes medications was tracked to account for potential diabetes-related confounding. To evaluate potential heterogeneity in the effect of metformin, prespecified stratified analyses were performed by HNC type (OPSCC or other) and age (≤60 or >60 years). Patients younger than 60 have been found to have a higher incidence of HPV-related HNC and an associated favourable prognosis.[29,30] Preclinical models of oral squamous cell carcinomas have been found to express organic cation transporter 3, responsible for uptake of metformin into HNC cells, and may be necessary for antineoplastic activity.[14,31]

This study was determined not to constitute human subjects research by the Thomas Jefferson University Institutional Review Board.

3 | RESULTS AND DISCUSSION

During the study period, 8392 individuals were diagnosed with HNC, of whom 7872 met all inclusion criteria. Among included patients, 436 (5.5%) were exposed to metformin and 456 (5.8%) were exposed to other diabetes medications prior to being diagnosed (Table 1), while 708 (9.0%) patients were exposed to metformin after HNC diagnosis (Online Appendix S8). More than three-quarters of the population was male (75.6%) and the median age at diagnosis was 68.1 (1st Quartile 59.3, 3rd Quartile 76.7; Table 1). The incidence of HNC remained largely consistent over the 9-year study period. The

TABLE 1 Patient characteristics at HNC diagnosis (N = 7872)

Demographics	
Age at HNC diagnosis, y	
Median (1st, 3rd quartiles)	68.1 (59.3, 76.7)
Sex (female), n (%)	1918 (24.4)
Year of HNC diagnosis, n (%)	
2003-2005	2771 (35.2)
2006-2008	2585 (32.8)
2009-2011	2516 (32.0)
Geography[a], n (%)	
Hill	2076 (26.4)
Mountain	452 (5.7)
Plain	5344 (67.9)
HNC related variables	
Metastatic, n (%)	1285 (16.3)
Tumour resection, n (%)	5528 (70.2)
Chemotherapy, n (%)	2549 (32.4)
Radiotherapy, n (%)	3822 (48.6)
Cancer of the larynx, n (%)	3192 (40.6)
OPSCC, n (%)	873 (11.1)
Comorbidity	
Elixhauser comorbidities count[b]	
Median (1st, 3rd quartiles, max)	0 (0, 1, 7)
Drug exposures in year prior to HNC diagnosis[c]	
Metformin, n (%)	436 (5.5)
Other oral diabetes medications[d], n (%)	348 (4.4)
Insulin, n (%)	149 (1.9)
Aspirin, n (%)	1852 (23.5)
Beta-blockers, n (%)	1331 (16.9)
NSAIDs, n (%)	2187 (27.9)
ACE inhibitors or ARBs, n (%)	2880 (36.6)
Statins, n (%)	1267 (16.1)
Time from HNC diagnosis to end of follow-up, mo	
Median (1st, 3rd quartiles)	35.2 (15.3, 68.3)
All-cause mortality, n (%)	3626 (46.1)
Within 2 y of HNC diagnosis, n	2251
After 2 y of HNC diagnosis, n	1375
All-cause mortality among the 2110 aged ≤60 y at HNC diagnosis, n (%)	745 (35.3)
Within 2 y of HNC diagnosis, n	480
After 2 y of HNC diagnosis, n	265

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HNC, head and neck cancer; OPSCC, oropharyngeal squamous cell carcinoma.

[a]Geography is an indicator of population density and rurality.

[b]The complete list of all 30 comorbidity indicators summed-up to compose this score was described in detail by Elixhauser et al.[28]

[c]Patients exposed during at least one quarter in the year prior to the index quarter.

[d]Sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, meglitinides and incretin mimetics.

proportion of patients with cancers of the larynx and OPSCC was 40.6% and 11.1%, respectively.

Over a median follow-up duration of 35.2 months (15.3, 68.3), a total of 3626 (46.1%) patients died from any cause. Nearly, a sixth of patients (16.3%) presented with metastatic disease. Treatment (alone or in combination) included tumour resection for the majority (70.2%) of patients, with 48.6% and 32.4% of patients receiving radiotherapy and chemotherapy, respectively.

In the adjusted model (Table 2), the all-cause mortality rate among metformin exposed patients was 0.81 (95% CI: 0.61-1.09) times the rate among unexposed patients during the period 0-2 years post-diagnosis, while the all-cause mortality rate appeared to be higher (HR: 1.20, 95% CI: 0.94-1.53) among metformin exposed patients for the period ≥2 years post-diagnosis. Crude model results were similar (HR 0-2 years: 0.89, 95% CI: 0.75-1.06; HR ≥2 years: 1.45, 95% CI: 1.13-1.85). In the multivariable model, metformin exposure prior to the diagnosis of HNC was not associated with survival (HR: 1.06, 95% CI 0.81-1.39). Post-index exposure to insulin was associated with a higher rate of death (HR: 1.89, 95% CI: 1.55-2.31). Among the other medication classes included in the model due to potential relevance in cancer survival, post-index exposure to statins (HR: 0.81, 95% CI: 0.71-0.93) and other oral diabetes medications (HR: 0.79; 95% CI: 0.64-0.97) were found to have protective associations.

The primary model results were consistent in the a priori specified, clinically motivated sensitivity analysis among patients with OPSCC (HR for the period of 0-2 years post-diagnosis: 0.83, 95% CI 0.33-2.07; HR for the period ≥2 years post-diagnosis: 1.48, 95% CI 0.65-3.37) and without OPSCC (HR for the period of 0-2 years post-diagnosis: 0.81, 95% CI 0.60-1.12; HR for the period ≥2 years post-diagnosis: 1.20, 95% CI 0.93-1.55). However, the association between metformin and survival was stronger in the subgroup of patients 60 years of age and younger (HR for the period of 0-2 years post-diagnosis: 0.22, 95% CI 0.09-0.56; HR for the period ≥2 years post-diagnosis: 0.56, 95% CI 0.26-1.22) and was attenuated in those over 60 years of age (HR for the period of 0-2 years post-diagnosis: 0.98, 95% CI 0.72-1.34; HR for the period ≥2 years post-diagnosis: 1.30, 95% CI 1.01-1.69).

In this large population-based study, exposure to the hypoglycaemic agent metformin after a diagnosis of HNC was found to have a modest protective association with survival in the first 2 years after the HNC diagnosis. This association was stronger in the subgroup of patients 60 years of age and younger. The relatively short median follow-up of 35 months in the context of a 10-year longitudinal investigation emphasizes the significant mortality burden in this population, as nearly half of the cohort died during follow-up. Although metformin did not exhibit a consistent relationship with survival over the entirety of follow-up, the magnitude and the timing of the shift in the hazard ratio are clinically intuitive.

Considering the increased risk of medical complications and death among patients with diabetes,[32] and that these risks increase with diabetes duration,[22] it is feasible that the evolution of the hazard ratio reflects an initial benefit of metformin use during active HNC followed by prevailing higher rates of mortality for metformin exposed patients due to the acceleration of cancer and non-cancer causes of death by diabetes-related processes. Further, limited preclinical evidence suggests metformin could exhibit complementary activity (eg, as a radiosensitizer) when exposure coincides with or closely follows other treatment modalities.[33] This early post-diagnosis window is the relevant time period when a clinical intervention would be considered, and our findings support further investigation of a possible adjuvant role for metformin in slowing progression or recurrence of HNC.

Findings from a recent evaluation of the influence of diabetes on all-cause mortality in HNC patients were consistent with the existence of opposing effects of diabetes severity and metformin (or other diabetes medication) exposure on survival.[34] The study did not consider diabetes medication exposures or diabetes severity. Therefore, the effect estimate comparing patients with diabetes to those without diabetes implicitly estimated an average effect where any benefit of drug exposures and any negative effect of diabetes severity would have at least partially cancelled. The authors expressed surprise at unexpectedly similar 5-year survival rates in diabetes and non-diabetes patients in light of older age and greater comorbidity burden among the patients with diabetes.[34] The effects of other oral diabetes medications may also be relevant, as oral diabetes medications were found to be protective in our study.

Reviews of the metformin literature have attempted to consolidate findings from studies which have applied different analytic approaches with varying degrees of bias across several cancer types. One meta-analysis of observational studies investigating the association between metformin and death from cancer observed a 35% reduction in the risk of cancer mortality.[35] Studies with known biases acknowledged by the review authors were included in the primary effect estimate from the meta-analysis.[35] A second systematic review and meta-analysis evaluated metformin use across 21 observational studies that used a comparison group of patients with diabetes and reported a pooled hazard ratio of similar magnitude (HR 0.73).[36] However, sensitivity analyses found an attenuated association (HR: 0.87) within four studies adjusting for diabetes severity.[36]

Multiple publications have drawn attention to pervasive time biases (immortal time bias, disease duration differences or time-lag bias) in the early metformin literature.[16,37] Time-dependent modelling has since been applied in some studies to avoid immortal time bias.[19-21] However, immortal time bias obscured the true association in a recent observational study reporting beneficial effects of metformin on HNC-specific survival.[25] In addition to accounting for time biases, the choice of a comparison group is critical to minimize bias from disease severity differences, as illustrated in a study evaluating metformin and survival among colorectal cancer patients.[21] Patients with any metformin exposure in the year prior to diagnosis had a 31% reduced risk of all-cause mortality compared with patients with diabetes exposed to at least one non-metformin antidiabetic prescription. A separate all-cause mortality model, analogous to our approach in HNC, estimated the metformin-survival association in the full cohort of colorectal cancer patients and found an attenuated association.[21] Although full cohort comparisons also are likely to

TABLE 2 Time-dependent metformin exposures evaluated in a multivariable Cox proportional hazards model of all-cause mortality following HNC diagnosis

Variable	HR	95% CI
Time-dependent metformin exposure after HNC diagnosis[a]		
During the first 2 y of survival	0.81	0.61, 1.09
After surviving two or more years	1.20	0.94, 1.53
HNC related		
Metastatic	2.64	2.45, 2.85
Tumour resection	0.78	0.72, 0.84
Chemotherapy	2.52	2.31, 2.75
Radiotherapy	1.52	1.41, 1.64
Cancer of the larynx	0.88	0.82, 0.95
OPSCC	0.70	0.63, 0.78
Demographics		
Age/10 y at HNC diagnosis	1.62	1.57, 1.67
Age/10 y squared	1.10	1.08, 1.12
Sex (male)	1.17	1.08, 1.27
Diagnosis calendar time (y)	0.99	0.98, 1.00
Geography		
Hill vs Plain	1.02	0.95, 1.10
Mountain vs Plain	1.23	1.08, 1.41
Comorbidity		
Elixhauser comorbidity score[b]	1.34	1.30, 1.38
Other drug exposures after HNC diagnosis[a]		
Aspirin	1.08	0.97, 1.20
ACE inhibitors/ARBs	1.01	0.90, 1.14
Beta-blockers	1.31	1.16, 1.48
NSAIDs	1.27	1.17, 1.38
Statins	0.79	0.68, 0.92
Other oral diabetes medications[c]	0.79	0.64, 0.97
Insulin	1.89	1.55, 2.31
Drug exposures in year prior to HNC diagnosis		
Metformin	1.06	0.81, 1.39
Aspirin	1.02	0.91, 1.15
ACE inhibitors/ARBs	0.90	0.80, 1.02
Beta-blockers	0.80	0.69, 0.91
NSAIDs	0.89	0.81, 0.97
Statins	0.93	0.78, 1.11
Other oral diabetes medications[c]	1.07	0.78, 1.11
Insulin	0.81	0.61, 1.08

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HNC, head and neck cancer; HR, hazard ratio; CI, confidence interval.
[a]Exposure to a particular drug class for any given quarter-year period after HNC diagnosis was indicated if the patient received at least one prescription from that drug class in the previous quarter or any previous post-index quarter. A significant time-dependency was detected and a parameter was added to the model to characterize how the association between metformin and HNC survival changes at year 2 ($P = 0.002$).
[b]The complete list of all 30 comorbidity indicators summed to compose this score was described in detail by Elixhauser et al.[28]
[c]Sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, meglitinides and incretin mimetics.

introduce bias (most non-users will not have diabetes), the direction of this bias is well-established as against metformin.

Despite supportive preclinical evidence in oral squamous cell carcinomas,[14,31,33] we did not observe heterogeneity in the metformin-survival association between patients with and without OPSCC. The apparent heterogeneity in the metformin-survival association by age may reflect effect modification due to differences in underlying pharmacology and disease aetiology, confounding by diabetes duration/severity (ie, any beneficial effect of metformin was outweighed by the deleterious effects of diabetes on HNC survival in older patients but not in younger patients with shorter diabetes duration) and/or confounding due to other unobserved factors. One single-centre study reported modest non-significant protective associations between metformin and HNC recurrence, all-cause mortality, and HNC-specific mortality.[24] Another single-centre study of metformin in laryngeal squamous cell carcinoma reported a survival benefit, however the true association was obscured by immortal time bias.[23] An ongoing single-arm prospective study is examining metformin with cisplatin and radiation for locally advanced HNC.[38]

In the present study, exposure to statins and exposure to other oral diabetes medications in the post-diagnosis period were associated with lower all-cause mortality. Although methods of exposure classification were conserved between metformin and other drug classes in the model, the association with all-cause mortality for these medications was not a primary estimate of interest and must be interpreted with caution. Preclinical studies of statins in HNC have reported reduced colony formation and metastasis,[39,40] suggesting future observational studies of statin exposure and HNC survival may be warranted.

In this retrospective observational study, the timing and assignment of metformin treatment after HNC diagnosis were not determined by the investigators as in a prospective trial. However, by evaluating the relationship between metformin exposure and survival in the first 2 years post-diagnosis separately from the remainder of follow-up, we were able to empirically isolate the period when an intervention appears most likely to confer benefit. Outpatient diagnoses are not available in the database; therefore, we established an index date based upon the first hospital record with a HNC diagnosis. Despite adjustments, the comparison of metformin exposed and unexposed patients with HNC may have been affected by residual confounding due to the severity of disease differences or unobserved characteristics (eg, smoking, obesity). However, we adjusted for indicators of HNC site, metastases, treatment (resection, radiotherapy, chemotherapy), and for use of other diabetes medications. To the extent residual confounding from diabetes remained, available evidence suggests patients with cancer and diabetes have increased mortality risk compared with cancer patients without diabetes.[41]

4 | WHAT IS NEW AND CONCLUSION

The present study of all-cause mortality is believed to be the largest population-based study to date of metformin exposure after

diagnosis of HNC. Our methods addressed potential biases from immortal time and disease severity that have been common in pharmacoepidemiologic studies of metformin. The universal healthcare structure in Italy provided an entire population for longitudinal study over a 10-year period with limited censoring. Our findings suggested metformin exposure was associated with a lower rate of all-cause mortality during the 2-year period after diagnosis, and that this association was concentrated among younger patients. This signal warrants cautious interpretation in light of the limitations of administrative data and requires replication in other patient populations and data sources. The repurposing of safe, widely available generic medications such as metformin for use in cancer treatment represents an attractive scenario for patients, providers and payers. Methodologically rigorous preclinical and observational investigations are important for the evaluation of anti-cancer activity before such strategies can be implemented in the clinic. Additional clinical and observational studies are needed to better understand metformin's influence on HNC survival.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA ACCESSIBILITY

Data for this study were retrieved from the Regional database of the Emilia-Romagna Region, provided through a collaborative agreement between the Regional Health Care and Social Agency, Regione Emilia-Romagna, Italy, the Health Care Authority, Regione Emilia-Romagna, Italy, and Thomas Jefferson University.

REFERENCES

1. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;83:489-501.
2. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst*. 2011;103(2):117-128.
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
4. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-1956.
5. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med*. 2008;359:1143-1154.
6. Bose P, Brockton NT, Dort JC. Head and neck cancer: from anatomy to biology. *Int J Cancer*. 2013;133:2013-2023.
7. Zhang H, Dziegielewski PT, Biron VL, et al. Survival outcomes of patients with advanced oral cavity squamous cell carcinoma treated with multimodal therapy: a multi-institutional analysis. *J Otolaryngol Head Neck Surg*. 2013;42:30.
8. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937-1944.
9. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350:1945-1952.
10. Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA. The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. *Cell Cycle*. 2009;8:88-96.
11. Ben Sahra I, Laurent K, Giuliano S, et al. Targeting cancer cell metabolism: the combination of metformin and 2-deoxyglucose induces p53-dependent apoptosis in prostate cancer cells. *Cancer Res*. 2010;70:2465-2475.
12. Fendt SM, Bell EL, Keibler MA, et al. Metformin decreases glucose oxidation and increases the dependency of prostate cancer cells on reductive glutamine metabolism. *Cancer Res*. 2009;73:4429-4438.
13. Vitale-Cross L, Molinolo AA, Martin D, et al. Metformin prevents the development of oral squamous cell carcinomas from carcinogen-induced premalignant lesions. *Cancer Prev Res (Phila)*. 2012;5(4):562-573.
14. Patel H, Younis RH, Ord RA, Basile JR, Schneider A. Differential expression of organic cation transporter OCT-3 in oral premalignant and malignant lesions: potential implications in the antineoplastic effects of metformin. *J Oral Pathol Med*. 2013;42(3):250-256.
15. Luo Q, Hu D, Hu S, Yan M, Sun Z, Chen F. In vitro and in vivo anti-tumor effect of metformin as a novel therapeutic agent in human oral squamous cell carcinoma. *BMC Cancer*. 2012;12:517.
16. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care*. 2012;35(12):2665-2673.
17. Azoulay L, Dell'Aniello S, Gagnon B, Pollak M, Suissa S. Metformin and the incidence of prostate cancer in patients with type 2 diabetes. *Cancer Epidemiol Biomarkers Prev*. 2011;20(2):337-344.
18. Smiechowski BB, Azoulay L, Yin H, Pollak MN, Suissa S. The use of metformin and the incidence of lung cancer in patients with type 2 diabetes. *Diabetes Care*. 2013;36(1):124-129.
19. Lega IC, Austin PC, Gruneir A, Goodwin PJ, Rochon PA, Lipscombe LL. Association between metformin therapy and mortality after breast cancer: a population-based study. *Diabetes Care*. 2013;36(10):3018-3026.
20. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J Clin Oncol*. 2013;31(25):3069-3075.
21. Spillane S, Bennett K, Sharp L, Barron TI. A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2013;22(8):1364-1373.
22. Zoungas S, Woodward M, Li Q, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia*. 2014;57(12):2465-2474.
23. Sandulache VC, Hamblin JS, Skinner HD, Kubik MW, Myers JN, Zevallos JP. Association between metformin use and improved survival in patients with laryngeal squamous cell carcinoma. *Head Neck*. 2014;36(7):1039-1043.
24. Kwon M, Roh JL, Song J, et al. Effect of metformin on progression of head and neck cancers, occurrence of second primary cancers, and cause-specific survival. *Oncologist*. 2015;20(5):546-553.
25. Stokes WA, Eguchi M, Amini A, et al. Survival impact and toxicity of metformin in head and neck cancer: an analysis of the SEER-Medicare dataset. *Oral Oncol*. 2018;84:12-19.
26. Sikirica S, Marino M, Gagne JJ, De Palma R, Maio V. Risk of death associated with the use of conventional vs. atypical antipsychotic medications: evaluating the use of the Emilia-Romagna Region database for pharmacoepidemiological studies. *J Clin Pharm Ther*. 2014;39(1):38-44.
27. Clancy Z, Keith SW, Rabinowitz C. Statins and colorectal cancer risk: a longitudinal study. *Cancer Causes Control*. 2013;24(4):777-782.
28. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27.

29. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008;26(4):612-619.
30. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.
31. Madera D, Vitale-Cross L, Martin D, et al. Prevention of tumor growth driven by PIK3CA and HPV oncogenes by targeting mTOR signaling with metformin in oral squamous carcinomas expressing OCT3. *Cancer Prev Res (Phila)*. 2015;8(3):197-207.
32. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States, 2014*. Atlanta, GA: U.S. Department of Health and Human Services; 2014.
33. Rêgo DF, Elias ST, Amato AA, Canto GL, Guerra EN. Anti-tumor effects of metformin on head and neck carcinoma cell lines: A systematic review. *Oncol Lett*. 2017;13(2):554-566.
34. Foreman A, Lee DJ, McMullen C, et al. Impact of type 2 diabetes mellitus on survival in head and neck squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 2017;157(4):657-663.
35. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. *PLoS ONE*. 2013;8(8):e71583.
36. Lega IC, Shah PS, Margel D, Beyene J, Rochon PA, Lipscombe LL. The effect of metformin on mortality following cancer among patients with diabetes. *Cancer Epidemiol Biomarkers Prev*. 2014;23(10):1974-1984.
37. Suissa S, Azoulay L. Metformin and cancer: mounting evidence against an association. *Diabetes Care*. 2014;37(7):1786-1788.
38. Dose-finding study of metformin with chemoradiation in locally advanced head and neck squamous cell carcinoma. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02325401. http://clinicaltrials.gov/ct/show/NCT00287391?order=1. Accessed July 29, 2017.
39. Islam M, Sharma S, Kumar B, Teknos TN. Atorvastatin inhibits RhoC function and limits head and neck cancer metastasis. Atorvastatin inhibits RhoC function and limits head and neck cancer metastasis. *Oral Oncol*. 2013;49(8):778-786.
40. Stoehr M, Mozet C, Boehm A, Aigner A, Dietz A, Wichmann G. Simvastatin suppresses head and neck squamous cell carcinoma ex vivo and enhances the cytostatic effects of chemotherapeutics. *Cancer Chemother Pharmacol*. 2014;73(4):827-837.
41. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA*. 2008;300(23):2754-2764.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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