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Dipeptidyl peptidase-4 inhibitors and the risk of skin cancer among patients with type 2 diabetes: a UK population-based cohort study

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ABSTRACT

Introduction The dipeptidyl peptidase-4 (DPP-4) enzyme significantly influences carcinogenic pathways in the skin. The objective of this study was to determine whether DPP-4 inhibitors are associated with the incidence of melanoma and nonmelanoma skin cancer, compared with sulfonylureas.

Research design and methods Using the United Kingdom Clinical Practice Research Datalink, we assembled two new-user active comparator cohorts for each skin cancer outcome from 2007 to 2019. For melanoma, the cohort included 96 739 DPP-4 inhibitor users and 209 341 sulfonylurea users, and 96 411 DPP-4 inhibitor users and 208 626 sulfonylurea users for non-melanoma skin cancer. Propensity score fine stratification weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs of melanoma and non-melanoma skin cancer, separately.

Results Overall, DPP-4 inhibitors were associated with a 23% decreased risk of melanoma compared with sulfonylureas (49.7 vs 65.3 per 100 000 person-years, respectively; HR 0.77, 95% CI 0.61 to 0.96). The HR progressively reduced with increasing cumulative duration of use (0–2 years HR 1.14, 95% CI 0.84 to 1.54; 2.1–5 years HR 0.44, 95% CI 0.29 to 0.66; >5 years HR 0.33, 95% CI 0.14 to 0.74). In contrast, these drugs were not associated with the incidence of non-melanoma skin cancer, compared with sulfonylureas (448.1 vs 426.1 per 100 000 person-years, respectively; HR 1.06, 95% CI 0.98 to 1.15).

Conclusions In this large, population-based cohort study, DPP-4 inhibitors were associated with a reduced risk of melanoma but not non-melanoma skin cancer, compared with sulfonylureas.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The dipeptidyl peptidase-4 (DPP-4) molecule influences biological pathways involved in skin carcinogenesis.
⇒ We investigated whether DPP-4 inhibitors are associated with the risk of melanoma and non-melanoma skin cancer

WHAT THIS STUDY ADDS

⇒ Compared with sulfonylurea use, DPP-4 inhibitor new users had a 23% lower risk of melanoma.
⇒ The risk reduction was pronounced after 2 years of use.
⇒ DPP-4 inhibitor use was not associated with the incidence of non-melanoma skin cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The finding that DPP-4 inhibitors were not associated with skin cancer is reassuring, while the preventive effect of these drugs on melanoma needs corroboration in future studies

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are antihyperglycemic drugs used as second-line to third-line treatment in type 2 diabetes.[1 2] With their rising use, previously unanticipated beneficial as well as adverse effects, including a potential association with skin cancer,[3] have emerged.[4]

Skin cancer, including melanoma and non-melanoma skin cancer, represents the most common human malignancy.[5] Despite recent progress,[6] melanoma entails a poor prognosis,[7] while non-melanoma skin cancer disproportionately impacts the underprivileged,[8–10] highlighting the continued need for cost-effective preventive and therapeutic strategies. Whether DPP-4 inhibitors impact skin cancer incidence warrants investigation given the involvement of the DPP-4 enzyme in skin cancer pathogenesis.[11] Indeed, pharmacological DPP-4 inhibition in mice reduces melanoma growth by trafficking antitumor lymphocytes.[12] In non-melanoma skin cancer, DPP-4 enzyme activity is variable.[3 13] In one meta-analysis of randomized controlled trials (RCTs), DPP-4 inhibitors imparted a lower risk of skin cancer (OR 0.85, 95% CIs 0.72 to 0.99),[14] although in two other meta-analyses, no such association was found.[15 16] To our knowledge,

no real-world study has examined the association between DPP-4 inhibitor use and skin cancer.

Thus, the objective of this study was to determine whether the use of DPP-4 inhibitors is associated with the incidence of melanoma and non-melanoma skin cancer, separately, among patients with type 2 diabetes, compared with use of sulfonylureas, another class of second-line to third-line antihyperglycemic drugs.[1 2]

METHODS

Data source

We used the Clinical Practice Research Datalink (CPRD), a representative, electronic health records database containing detailed information for more than 50 million patients seen at over 2000 general practices in the UK.[17] In this database, clinical diagnoses are recorded using Read and SNOMED-CT classification system and drug prescriptions are recorded using UK Prescription Pricing Authority Dictionary.[17] Importantly, this database also records lifestyle, clinical, and anthropometric variables. These variables have been validated and the data and practices are audited regularly to ensure high quality.[18–21]

Study population

We assembled two new-user, active comparator cohorts, each investigating a specific skin cancer outcome, from January 1, 2007 (the year the first DPP-4 inhibitors entered the UK market) through July 31, 2019. These cohorts compared initiators of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) with initiators of sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, and tolbutamide). Cohort entry was defined by the date of either the first prescription of a DPP-4 inhibitor or a sulfonylurea during the study period. Patients below 18 years of age, those having concomitant use of the study drugs at cohort entry, and those with less than 1 year of medical history in the CPRD before cohort entry were excluded. The latter served as a washout period to identify new users. We then excluded patients previously diagnosed with any type of skin cancer ever before cohort entry and those with end-stage renal disease as it constitutes a relative contraindication to sulfonylurea use. We also excluded patients with a history of use of the study drugs (DPP-4 inhibitors and sulfonylureas), as well as glucagon-like peptide-1 receptor agonist users, as these drugs share a similar mechanism of action with DPP-4 inhibitors.[22] Finally, we excluded patients with less than 1 year of follow-up for cancer latency purposes (ie, lag period). Patients diagnosed with the skin cancer of interest during this lag period were excluded, resulting in two cohorts, one specific to each outcome of interest.

We used sulfonylureas as the comparator as they are widely used second-line to third-line drugs among patients with type 2 diabetes,[2] and have not been linked to skin cancer in both clinical[23] and laboratory settings.[24] We did not use other comparators such as metformin (typically initiated at early stage of the disease), insulin (used at an advanced stage), thiazolidinediones (as they are infrequently used due to their association with serious adverse events), GLP-1 receptor agonists (which have been potentially linked with skin cancers), or sodium glucose co-transporter-2 inhibitors (which are relatively new molecules whose use would have restricted the cohort to 2013 and later, which would be prohibitive due to small sample size).

Follow-up

All patients were followed starting 1 year after cohort entry (ie, after the lag period) until an incident diagnosis of the skin cancer of interest, 1 year after switching to one of the study drugs, death from any cause, end of registration with the general practice, or the end of the study period (July 31, 2020), whichever occurred first. Melanoma diagnoses have been previously validated in the CPRD, with a positive predictive value of 85% compared with medical review.[25] On the other hand, CPRD has a better documentation of non-melanoma skin cancer, including basal cell carcinoma and cutaneous squamous cell carcinoma, than the UK national cancer registry.[26 27] Moreover, validation studies of UK primary care databases have shown the positive predictive value to be 93%[28] and 83%[29] for basal cell carcinoma and cutaneous squamous cell carcinoma, respectively.

Potential confounders

We considered a wide range of potential confounders, all measured before or at cohort entry. These included age (modeled using cubic splines with five interior knots to account for a possible non-linear relation with the exposure), sex, lifestyle-related factors (body mass index, alcohol-related disorders, smoking status), calendar year (as a proxy for temporal trends in prescribing and changes in ultraviolet radiation, categorized as 2007–2010, 2011–2014, 2015–2019) and region (as a proxy for exposure to sunlight). We considered known skin cancer risk factors, including precancerous photodermatoses (serving as markers of sun exposure), and use of photosensitizing and immunosuppressive drugs. We also considered diabetes-related variables such as hemoglobin A1c (HbA1c), duration of diabetes (calculated as the time between cohort entry and the earliest of a diabetes diagnosis, use of an antihyperglycemic drug, or an HbA1c value of ≥ 6.5%), as well as microvascular (nephropathy, neuropathy, retinopathy) and macrovascular (myocardial infarction, stroke, peripheral arteriopathy) complications of diabetes. Furthermore, we adjusted for the use of antihyperglycemic drugs even before cohort entry (including metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, sodium-glucose cotransporter-2 inhibitors, and insulin), common comorbidities (heart failure, cancer, obstructive sleep apnea, osteoarthritis, chronic obstructive pulmonary disease, depression, dyslipidemia, gastrointestinal reflux disease, cardiac arrhythmia, hypertension, hypothyroidism) and co-medications (antihypertensives, antiarrhythmics, antiplatelet

agents, statins, non-steroidal anti-inflammatory drugs, corticosteroids, biologics, proton pump inhibitors), and markers of healthcare-seeking behavior (uptake of cancer screening (fecal occult blood testing or colonoscopy, mammography, prostate-specific antigen testing) and vaccinations (including influenza and pneumococcal vaccinations) in the year before cohort entry).

Statistical analysis

We used propensity score fine stratification to adjust for confounding.[30] In each cohort, we estimated the predicted probability of receiving a DPP-4 inhibitor versus a sulfonylurea by using multivariable logistic regression conditional on the covariates listed above. After trimming patients in the non-overlapping regions of the propensity score distributions, we created 50 strata based on the propensity score distribution of the DPP-4 inhibitor users. In each stratum, DPP-4 inhibitor users were assigned a weight of 1, while sulfonylurea users were weighted in proportion to the number exposed in the corresponding stratum. This method estimates the average treatment effect among the treated, that is, the DPP-4 inhibitor group.

We used descriptive statistics to summarize the exposure groups' characteristics before and after weighting. Covariate balance before and after weighting were assessed using standardized differences, with a difference of less than 0.10 indicative of good balance.[31] Weighted incidence rates of melanoma and non-melanoma skin cancer, with 95% CIs based on the Poisson distribution, were calculated for each exposure group. Weighted Kaplan-Meier curves were used to display the cumulative incidence of melanoma and non-melanoma skin cancer for the exposure groups over the follow-up period. Finally, weighted Cox proportional hazards models were fit to estimate HRs with 95% CIs of incident melanoma and non-melanoma skin cancer in the respective cohorts, comparing DPP-4 inhibitors with sulfonylureas. We also calculated the number needed to treat/harm for both outcomes after 5 years of follow-up by applying the Kaplan-Meier method.[32]

Secondary analyses

We conducted four secondary analyses. In the first two analyses, we assessed whether the association varied with time since treatment initiation and cumulative duration of use of DPP-4 inhibitors. In these analyses, the exposure was defined in a time-varying manner, updated every person-day of follow-up. Specifically, the time since initiation was calculated as the difference between cohort entry date and end of follow-up, while the cumulative duration of use was the sum of prescription durations since cohort entry until the risk set event. In the third analysis, we assessed whether the association varied with individual drugs (sitagliptin, alogliptin, saxagliptin, linagliptin, vildagliptin). Lastly, we examined potential effect measure modification on the multiplicative scale by age (<65 vs ≥ 65 years), sex, and use of immunosuppressive drugs. Effect modification was tested by including interaction terms between exposures and these variables in the models.

Sensitivity analyses

We conducted two sensitivity analyses to assess the robustness of our findings. First, we repeated the analysis by lengthening the exposure lag period to 3 years and 5 years to address uncertainties regarding the appropriate duration of cancer latency. Second, we used stabilized inverse probability of censoring weighting to investigate the potential for informative censoring from (1) drug crossover or switching during follow-up and (2) competing risk of death from any cause.[33–35] All analyses were conducted with SAS V.9.4 (SAS institute, Cary, North Carolina, USA).

RESULTS

Melanoma outcome cohort

The melanoma outcome cohort included 96 739 new users of DPP-4 inhibitors and 209 341 new users of sulfonylureas (online supplemental figure 1). Before weighting, DPP-4 inhibitor users were more likely to be obese, have a longer duration of diabetes, have microvascular diseases, and enter at a later cohort entry year, than sulfonylurea users. After weighting, all covariates were well balanced, with the standardized difference varying between 0.01 to 0.03 (online supplemental table 1). Over a median follow-up of 2.6 years (IQR 1.1–5.0 years), a total of 634 melanoma events occurred generating a crude incidence rate of 60.5 per 100 000 person-years (95% CI 56.0 to 65.4).

After weighting, the use of DPP-4 inhibitors was associated with a 23% decrease in the incidence of melanoma compared with the use of sulfonylureas (49.7 vs 65.3 per 100 000 person-years, respectively; HR 0.77, 95% CI 0.61 to 0.96) (table 1). The cumulative incidence curves diverged after almost 2 years of use (online supplemental figure 2), with the number needed to treat being 880 at 5 years. The time since initiation analysis revealed no association early in the follow-up period (0–2 years HR 1.24, 95% CI 0.83 to 1.86), followed by HRs below the null value but with wide CIs (2.1–5 years HR 0.59, 95% CI 0.41 to 0.84; >5 years HR 0.69, 95% CI 0.42 to 1.13) (table 1). Similarly, with cumulative duration of use, the HRs decreased with longer durations of use, with at least 5 years of use associated with a 67% decreased hazard (HR 0.33, 95% CI 0.14 to 0.74) (table 1).

The results were consistent across the individual drugs, with HRs below null value with wide CIs, except sitagliptin (the most common DPP-4 inhibitor in the cohort), where the CIs excluded the null value (table 1). The association was not modified by age, sex, or prior use of immunosuppressants (online supplemental figure 3). Overall, the sensitivity analyses aligned with the primary results, although the inverse probability of censoring weighted analysis generated wide CIs (online supplemental figure 4).

Table 1 HR for melanoma comparing DPP-4 inhibitors with sulfonylureas

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI)†
Primary analysis						
Sulfonylureas	209 341	515	807 734	65.3 (58.9 to 72.1)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	96 739	119	239 306	49.7 (41.2 to 59.5)	0.81	0.77 (0.61 to 0.96)
Time since initiation						
0–2 years						
Sulfonylureas	209 341	100	189 832	50.0 (40.3 to 61.4)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	96 739	50	81 047	61.7 (45.8 to 81.3)	1.18	1.24 (0.83 to 1.86)
2.1–5 years						
Sulfonylureas	171 110	226	371 967	71.0 (62.1 to 80.8)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	66 433	48	115 603	41.5 (30.6 to 55.1)	0.68	0.59 (0.41 to 0.84)
>5 years						
Sulfonylureas	83 658	189	246 193	71.1 (59.4 to 84.4)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	19 803	21	42 882	49.0 (30.3 to 74.9)	0.66	0.69 (0.42 to 1.13)
Cumulative duration of use						
0–2 years						
Sulfonylureas	209 512	176	336 493	52.2 (44.8 to 60.5)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	96 830	78	132 332	58.9 (46.6 to 73.5)	1.14	1.14 (0.84 to 1.54)
2.1–5 years						
Sulfonylureas	114 053	172	194 958	88.2 (75.5 to 102.4)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	44 177	34	86 893	39.1 (27.1 to 54.7)	0.55	0.43 (0.29 to 0.66)
>5 years						
Sulfonylureas	36 575	43	41 008	104.9 (75.9 to 141.3)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	9559	7	20 145	34.7 (14.0 to 71.6)	41	0.33 (0.15 to 0.74)
Individual drugs						
Sulfonylureas	64 218	83	139 697	74.9 (60.4 to 91.7)	1.00 (Reference)	1.00 (Reference)
Alogliptin	13 804	12	19 959	60.1 (31.1 to 105.0)	1.00	0.83 (0.43 to 1.59)
Sulfonylureas	120 639	213	359 962	79.1 (68.8 to 90.5)	1.00 (Reference)	1.00 (Reference)
Linagliptin	19 746	20	38 358	52.1 (31.8 to 80.5)	0.88	0.67 (0.40 to 1.12)
Sulfonylureas	165 686	362	572 340	71.1 (63.9 to 78.8)	1.00 (Reference)	1.00 (Reference)
Saxagliptin	8380	15	24 258	61.8 (34.6 to 102.0)	1.01	0.88 (0.51 to 1.51)
Sulfonylureas	209 373	515	807 932	61.7 (55.9 to 68.1)	1.00 (Reference)	1.00 (Reference)
Sitagliptin	53 865	69	149 607	46.1 (35.9 to 58.4)	0.75	0.76 (0.58 to 0.99)
Sulfonylureas	206 643	511	799 710	65.3 (60.1 to 70.8)	1.00 (Reference)	1.00 (Reference)
Vildagliptin	3346	7	13 415	52.2 (21.0 to 107.5)	0.81	0.80 (0.38 to 1.70)

*Per 100 000 person-years.
†Weighted using propensity score fine stratification.
DPP-4, dipeptidyl peptidase.

Non-melanoma skin cancer outcome cohort

The non-melanoma skin cancer cohort included 96 411 DPP-4 inhibitor new users and 208 626 sulfonylurea new users (online supplemental figure 5). As noted in the melanoma cohort, there were imbalances in terms of obesity, microvascular diseases, diabetes duration, and cohort entry year. After weighting, the covariates were well balanced between the exposure groups (standardized difference between 0.01 to 0.03) (online supplemental table 2). There were 4702 non-melanoma skin cancer events during a median of 2.6 years (IQR 1.1–5.0 years), generating an incidence rate of 455.7 per 100 000 (95% CI 442.8 to 468.9) person-years.

Overall, the use of DPP-4 inhibitors was not associated with the incidence of non-melanoma skin cancer (448.1 vs 426.1 per 100 000 person-years, respectively; HR 1.06,

Table 2 HRs for non-melanoma skin cancer comparing DPP-4 inhibitors with sulfonylureas

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI)†
Primary analysis						
Sulfonylureas	208 626	3643	795 481	426.1 (409.5 to 443.1)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	96 411	1059	236 339	448.1 (421.5 to 475.9)	1.02	1.06 (0.98 to 1.15)
Time since initiation						
0–2 years						
Sulfonylureas	208 626	737	188 875	378.8 (351.0 to 408.3)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	96,.411	333	80 647	412.9 (369.8 to 459.7)	1.06	1.09 (0.93 to 1.28)
2.1–5 years						
Sulfonylureas	169 749	1620	367 147	402.9 (381.3 to 425.5)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	65 970	507	114 245	443.8 (406.0 to 484.2)	1.01	1.10 (0.98 to 1.24)
>5 years						
Sulfonylureas	82 072	1281	239 016	511.1 (478.5 to 545.3)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	19 431	219	41 670	525.6 (458.3 to 600.0)	0.99	1.04 (0.88 to 1.22)
Cumulative duration of use						
0–2 years						
Sulfonylureas	210 260	1299	333 747	389.1 (368.2 to 410.8)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	96 929	504	131 371	383.7 (350.9 to 418.7)	0.95	0.98 (0.87 to 1.11)
2.1–5 years						
Sulfonylureas	114 185	891	192 180	463.4 (433.5 to 494.9)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	44 225	454	85 595	530.4 (482.7 to 581.5)	1.12	1.16 (1.02 to 1.31)
>5 years						
Sulfonylureas	36 252	245	39 817	614.6 (540.0 to 696.6)	1.00 (Reference)	1.00 (Reference)
DPP-4 inhibitors	9413	101	19 440	519.6 (423.2 to 631.3)	0.85	0.85 (0.68 to 1.08)
Individual drugs						
Sulfonylureas	64 024	515	138 582	403.9 (369.2 to 441.0)	1.00 (Reference)	1.00 (Reference)
Alogliptin	13 752	80	19 819	403.6 (320.1 to 502.4)	1.11	1.02 (0.79 to 1.33)
Sulfonylureas	120 223	1476	355 686	578.3 (549.6 to 608.0)	1.00 (Reference)	1.00 (Reference)
Linagliptin	19 643	230	37 827	608.0 (532.0 to 692.0)	1.50	1.05 (0.89 to 1.29)
Sulfonylureas	165 100	2498	564 489	459.4 (440.8 to 478.6)	1.00 (Reference)	1.00 (Reference)
Saxagliptin	8353	115	23 927	480.6 (396.8 to 576.9)	1.10	1.05 (0.87 to 1.28)
Sulfonylureas	208 657	3642	795 682	384.0 (369.0 to 399.4)	1.00 (Reference)	1.00 (Reference)
Sitagliptin	53 716	588	147 806	397.8 (366.3 to 431.3)	0.90	1.05 (0.96 to 1.16)
Sulfonylureas	205 962	3604	787 607	411.7 (398.3 to 425.4)	1.00 (Reference)	1.00 (Reference)
Vildagliptin	3343	68	13 192	515.5 (400.3 to 653.5)	1.12	1.25 (0.98 to 1.60)

*Per 100 000 person-years.
†Weighted using propensity score fine stratification.
DPP-4, dipeptidyl peptidase.

95% CI 0.98 to 1.15) (table 2). The cumulative incidence curves overlapped throughout the follow-up period (online supplemental figure 6). The HR remained close to the null value in all categories of time since initiation analysis (0–2 years HR 1.09, 95% CI 0.93 to 1.28; 2.1–5 years HR 1.10, 95% CI 0.98 to 1.24; >5 years HR 1.04, 95% CI 0.88 to 1.22). Similarly, there was no consistent pattern with cumulative duration of use, with all HRs around the null value (0–2 years HR 0.98, 95% CI 0.87 to 1.11; 2.1–5 years HR 1.16, 95% CI 1.02 to 1.31; >5 years HR 0.85, 95% CI 0.68 to 1.08).

The analysis stratified by individual drugs generated effect estimates similar to the primary analysis, with CIs including the null value for all drugs (table 2). While there was a 13% increased hazard in the subgroup of patients above 65 years, the CIs overlapped with the

estimate for patients below 65 years (online supplemental figure 7). Effect measure modification by sex or immunosuppressant use was also not detected (online supplemental figure 7). Sensitivity analyses resulted in estimates largely overlapping with the primary analysis results (online supplemental figure 8).

DISCUSSION

The results of this population-based cohort study suggest that, compared with sulfonylureas, DPP-4 inhibitors were associated with a reduced risk of melanoma, with evidence of a duration-response relationship. In contrast, these drugs were not associated with non-melanoma skin cancer. Overall, these results remained consistent in several sensitivity analyses.

To our knowledge, no clinical study has examined the use of DPP-4 inhibitors and skin cancer as a stand-alone outcome. One meta-analysis of 72 RCTs including 35 768 patients on DPP-4 inhibitor and 33 319 on comparison drugs/placebo reported a numerically lower risk of malignant melanoma (relative risk 0.87, 95% CI 0.48 to 1.59) but a numerically higher risk of skin cancer overall (relative risk 1.79, 95% CI 0.86 to 3.71).[15] A larger meta-analysis of 115 RCTs with 65 740 patients in the DPP-4 inhibitor group and 56 221 in the control group reported a lower overall risk of cancer (OR 0.91, 95% CI 0.85 to 0.97), all skin cancers (OR 0.85, 95% CIs 0.72 to 0.99), and malignant skin cancer (OR 0.86, 95% CIs 0.73 to 1.00), although the type of skin cancer was not specified.[14] In another meta-analysis of 157 RCTs with 66 825 patients on DPP-4 inhibitor treatment and 61 524 patients in the control group, DPP-4 inhibitor use was not associated with melanoma (OR 1.13, 95% CI 0.73 to 1.00).[16] However, all meta-analyses included short-term studies (<52 weeks), which may be inadequate to examine cancer risk.[14 15] Our study found that DPP-4 inhibitor use was associated with a 23% lower risk of melanoma skin cancer, the risk reduction occurring after 2 years of use. We did not find any consistent association of DPP-4 inhibitor use with non-melanoma skin cancer.

The DPP-4 enzyme has a complex role in the melanocyte malignant transformation.[11 36] Potential benefit of DPP-4 inhibitors in melanoma can be explained by biological findings in murine models where sitagliptin delayed melanoma development, tumor growth, and metastasis by trafficking antitumor CXCR3+lymphocytes to the tumor site by locally elevating the chemokine CXCL10, a substrate of the DPP-4 enzyme.[12] Sitagliptin also improved tumorous response to checkpoint blockade.[12] Given that cutaneous lymphocyte trafficking is a clinically well-characterized effect of DPP-4 inhibitor use mediating skin reactions such as bullous pemphigoid,[37 38] this could be a potential mechanism behind a reduced melanoma incidence with DPP-4 inhibitors.

Interestingly, we did not find a change in the risk of non-melanoma skin cancer with DPP-4 inhibitor use. Indeed, DPP-4 enzyme activity in non-melanoma skin cancer is variable, with high activity noted in basal cell carcinomas while both high and low activity in squamous cell carcinomas.[3] Even the role of CXCR3 in non-melanoma skin cancer is unclear:[39] imiquimod, an immunomodulator effective in non-melanoma skin cancer, recruits CXCR3+lymphocytes.[40] In contrast, CXCR3 gene deletion lowers the incidence of skin tumors in mice, and CXCR3+lymphocyte recruitment promotes keratinocyte proliferation.[41] These variable roles of DPP-4 and CXCR3 on keratinocytes might explain the relatively null association between DPP-4 inhibitors and non-melanoma skin cancer.

Overall, our study has several strengths. First, we used the CPRD as our data source, a database that is largely representative of the UK population. Using this database also allowed us to examine well-validated outcome definitions. Second, we accrued one million person-years of follow-up in both cohorts, with a potential follow-up of 13 years for each cohort, making our study well powered to determine whether DPP-4 inhibitors are associated with skin cancer. Finally, we used a new-user, active comparator design which likely minimized confounding and detection bias at the design stage, as well as bias from the inclusion of prevalent users.[42]

Our study also has some limitations. First, exposure misclassification is possible because the CPRD does not directly record prescriptions written by specialists. However, this is unlikely to be an important source of misclassification since general practitioners almost entirely manage type 2 diabetes in the UK.[43] Second, it was not possible to assess sun exposure at the patient level, an important skin cancer risk factor. Reassuringly, sun exposure is not considered when prescribing an antihyperglycemic drug versus another. Nonetheless, we included several proxies for variations in sun exposure in the propensity score models, including various photodermatoses, calendar year and region. Third, there was substantial missingness in the variable ethnicity, an important risk factor for skin cancer. However, given it was not differentially distributed between exposure groups, it is unlikely to have been a major source of residual confounding. Fourth, the possibility that undiagnosed skin cancer was present in the study cohort before commencing the study drugs cannot be ruled out. However, to minimize this possibility we applied a lag period, counting cases at 1 (primary) and 3 or 5 (sensitivity) years after the beginning of follow-up, with similar findings. Finally, residual confounding is a possibility given the observational nature of this study. However, given that clinical studies on the DPP-4 inhibitors-skin cancer association were published after the study period, any channelling related to this outcome is unlikely.

In summary, DPP-4 inhibitor use was associated with a reduced risk of melanoma but not with the incidence of non-melanoma skin cancer. Given the high mortality associated with melanoma, and dearth of preventive strategies related to this malignancy, more research should be conducted to confirm our findings.

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Contributors All authors conceived and designed the study. LA acquired the data. RP and LA performed the statistical analyses. RWP provided statistical expertise and OHYY provided clinical expertise. All authors analysed and interpreted the data. RP wrote the manuscript, and all authors critically revised it. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. LA supervised the study and is the guarantor.

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Data availability statement Data is available upon request. This study is based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. Because electronic health records are classified as “sensitive data” by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the Clinical Practice Research Datalink (https://www.cprd.com).

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