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Original Article

Cancer-Specific Disproportionality Signals Associated with Metformin Versus Other Antidiabetic Agents: A Real-World Pharmacovigilance Analysis of FAERS

Daniel Obinna Eke[1], Jessica Awingosit Ayamyiya[2], Katabaazi Lillian Mirembe[3], Anthony Kosisochukwu Anyabuoke[4], Jacqueline Azodoh[5], Gloria Oluwabukunmi Oladapo[6]

[1]*Department of Nursing, Myrtle E. and Earl E. Walker College of Health Professions Maryville University of St. Louis, St. Louis, MO, USA*
[2]*Department of Cancer Clinical Trials, University of Colorado Anschutz Medical Campus, Aurora, CO, USA*
[3]*Department of Pharmacovigilance Specialist, Feyti Medical Group, Kampala, Uganda*
[4]*Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA*
[5]*College of Pharmacy, Campbell University, Buies Creek, NC, USA*
[6]*Department of Pharmacology, University of Ibadan, Ibadan, Nigeria*

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Corresponding author's email:
deke1@live.maryville.edu

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ABSTRACT

Background:

Type 2 diabetes mellitus is associated with an increased risk of several malignancies, prompting interest in the potential oncologic effects of antidiabetic therapies, particularly metformin. This study evaluated cancer-related adverse event reporting associated with metformin compared with other antidiabetic agents using real-world pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS) between Q1 2023 and Q4 2024. A disproportionality analysis was conducted on over 3.2 million reports, including 66,187 metformin cases and 55,257 comparator cases comprising GLP-1 receptor agonists, SGLT2 inhibitors, sulfonylureas, and insulin. Reporting odds ratios (ROR), proportional reporting ratios (PRR), information components (IC), and chi-squared tests were applied across twelve pre-specified cancer types.

Metformin was associated with significantly lower reporting of hepatocellular carcinoma (ROR 0.377, 95% CI 0.181–0.782) and pancreatic carcinoma (ROR 0.669, 95% CI 0.493–0.908). In contrast, increased reporting signals were observed for prostate cancer (ROR 2.065, 95% CI 1.435–2.972), leukaemia (ROR 2.388, 95% CI 1.155–4.939), and breast cancer (ROR 1.404, 95% CI 1.023–1.926). Drug-specific comparisons indicated relatively lower overall cancer reporting for metformin compared with sitagliptin and empagliflozin, but higher reporting compared with insulin. Temporal analyses demonstrated variability in reporting patterns across study quarters.

These findings represent disproportionality signals reflecting reporting associations rather than causal effects and may be influenced by reporting bias, residual confounding, and differences in healthcare utilization. Overall, the results suggest a heterogeneous, cancer-type-specific reporting profile for metformin and highlight the value of pharmacovigilance analyses in generating real-world safety signals. Further confirmation in prospective and mechanistic studies is required.

Keywords: Metformin; Cancer; Pharmacovigilance; FAERS; Disproportionality Analysis; Reporting Odds Ratio; Antidiabetic Agents; Drug Safety

Introduction

Type 2 diabetes mellitus (T2DM) affects over 537 million adults worldwide and is projected to affect 783 million by 2045, representing a major global health burden (International Diabetes Federation [1]). Beyond its metabolic consequences, T2DM is a well-established independent risk factor for several malignancies, including hepatocellular carcinoma (HCC), pancreatic cancer, colorectal cancer, and endometrial cancer, mediated through shared pathophysiologic mechanisms including hyperinsulinemia, chronic low-grade inflammation, oxidative stress, and dysregulation of the insulin-like growth factor (IGF) axis [2,3].

Metformin (1,1-dimethylbiguanide hydrochloride) is the most widely prescribed first-line pharmacotherapy for T2DM globally and is recommended by major clinical guidelines including those of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [4]. Beyond glycemic control, metformin has attracted extraordinary scientific interest as a potential anticancer agent. Its principal proposed mechanisms of anticancer action include: (1) activation of AMP-activated protein kinase (AMPK) with downstream inhibition of the mammalian target of rapamycin (mTOR) pathway, reducing protein synthesis and cellular proliferation[5]; (2) direct inhibition of mitochondrial respiratory chain complex I, reducing oxidative phosphorylation [6]; (3) suppression of IGF-1 and insulin receptor signaling[7]; and (4) anti-inflammatory effects through NF-κB inhibition [8].

Epidemiological studies have provided supporting, albeit inconsistent, evidence for metformin's oncologic benefits. A landmark observational study by Evans et al. (2005) first reported a significantly reduced cancer incidence in metformin-treated diabetic patients compared to those receiving other antidiabetic therapies[9]. Subsequent meta-analyses have confirmed reduced risks of HCC[10,11] colorectal cancer [12], and endometrial cancer [13] in metformin users. However, evidence from randomized controlled trials remains limited and inconsistent, and cancer-type-specific pharmacovigilance data from contemporary real-world reporting systems are scarce[14].

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting database containing over 20 million case reports submitted by healthcare professionals, patients, and manufacturers worldwide. Disproportionality analysis of FAERS data using metrics such as the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) is a validated approach for pharmacovigilance signal detection[15,16]. The Information Component (IC), derived from Bayesian confidence propagation neural networks, offers an additional measure of statistical surprise robust to sparse data[17]. These methods have been widely applied to detect adverse drug reactions and have been endorsed by regulatory agencies including the European Medicines Agency (EMA) and WHO Uppsala Monitoring Centre [18].

To date, few studies have systematically evaluated cancer-specific disproportionality signals for metformin versus active comparator antidiabetic agents using contemporary FAERS data, and none have examined drug-specific and temporal patterns across individual antidiabetic drug classes. This study aimed to: (1) evaluate cancer-specific adverse event reporting disproportionality for metformin versus other antidiabetic agents; (2) compare metformin individually against each comparator drug class; and (3) characterize quarterly temporal trends across the study period.

Methods

Data Source and Study Design

We conducted a retrospective pharmacovigilance disproportionality analysis using the publicly available FAERS database covering Q1 2023 through Q4 2024, comprising 3,293,301 unique adverse event case reports. FAERS collects spontaneous reports from healthcare professionals, consumers, and pharmaceutical manufacturers in accordance with FDA post-marketing surveillance regulations (21 CFR §314.80, §314.81) (FDA, 2023). Data were downloaded as quarterly ASCII files from the FDA's public FAERS portal. This study used only publicly available de-identified data; therefore, no institutional review board (IRB) approval or informed consent was required [19]. The study was conducted and reported in accordance with recommended pharmacovigilance reporting standards [20].

Drug Identification and Comparator Selection

An active comparator new-user design was employed to minimize confounding by indication, as all included comparators share the T2DM indication with metformin [21]. Cases were classified into two groups: (1) Metformin group — all cases with 'METFORMIN' in the drug name field (n=66,187); and (2) Comparator group — cases containing any of the following antidiabetic agents: sitagliptin (DPP-4 inhibitor), empagliflozin, dapagliflozin, canagliflozin (SGLT2 inhibitors), semaglutide, liraglutide (GLP-1 receptor agonists), glipizide, glimepiride (sulfonylureas), pioglitazone (thiazolidinedione), saxagliptin, or insulin/glargine (n=55,257). Drug name fields were standardized to uppercase[22]. Cases appearing in both groups were assigned to the metformin group as the drug of interest.

Outcome Definition

Cancer outcomes were identified using MedDRA Version 26 Preferred Terms (PTs) from the REAC dataset[23]. Twelve cancer types were pre-specified based on biological plausibility of metformin's known mechanisms and prior literature: pancreatic carcinoma, colorectal cancer, breast cancer, lung neoplasm malignant, hepatocellular carcinoma, bladder cancer, prostate cancer, ovarian cancer, gastric cancer, renal cell carcinoma, lymphoma, and leukaemia.

Statistical Analysis

For each cancer outcome, a 2×2 contingency table was constructed with cells: (a) drug of interest + cancer event, (b) drug of interest + other events, (c) comparator + cancer event, (d) comparator + other events. The following signal detection metrics were calculated [24,25]

- Reporting Odds Ratio (ROR) = (a/b)/(c/d) with 95% CI using the standard log-linear method
- Proportional Reporting Ratio (PRR) = [a/(a+b)] / [c/(c+d)]
- Information Component (IC) using Bayesian shrinkage: $IC = \log_2[(a+0.5)/(E+0.5)]$, where E = expected count
- Chi-squared test for independence with threshold $Chi^2>4$ and $p<0.05$

A positive disproportionality (risk) signal required: ROR>1 with lower 95% CI bound >1, $Chi^2>4$, and $p<0.05$. A protective signal required: ROR<1 with upper 95% CI bound <1, $Chi^2>4$, and $p<0.05$. These criteria are consistent with established pharmacovigilance signal detection standards[20,26]. Minimum case threshold of n≥5 in both groups was applied to ensure statistical stability[27]. All analyses were performed in Python 3.14 (Python Software Foundation)(28) using pandas[28], numpy[29], and scipy [30] libraries. Visualizations were generated with matplotlib[31] and seaborn[32].

Results

Study Population

A total of 3,293,301 unique adverse event reports were identified in FAERS from Q1 2023 to Q4 2024. The metformin group comprised 66,187 cases and the comparator antidiabetic group comprised 55,257 cases. Demographic characteristics are summarized in Table 1. The metformin group was predominantly female (54.0%) with a corrected mean age of 63.4 ± 14.2 years and median of 65.0 years. The comparator group showed a higher proportion of males (51.3%) and comparable median age of 66.0 years. The United States was the top reporting country for both groups, consistent with FAERS reporting patterns[19]. A total of 631 (0.95%) metformin cases and 315 (0.57%) comparator cases were associated with the 12 pre-specified cancer outcomes.

Table 1. Baseline Characteristics of Study Groups — FDA FAERS, Q1 2023–Q4 2024

Characteristic	Metformin (n=66,187)	Comparators (n=55,257)
Sex — Male, n (%)	29,830 (45.1%)	28,347 (51.3%)
Sex — Female, n (%)	35,741 (54.0%)	26,744 (48.4%)
Age — Mean ± SD (years)	63.4 ± 14.2	64.2 ± 15.3
Age — Median (years)	65.0	66.0
Age <40 years, %	6.3%	7.0%
Age 40–60 years, %	27.4%	25.4%
Age 60–75 years, %	44.0%	40.9%
Age ≥75 years, %	22.4%	26.7%
Missing age data, %	29.4%	30.0%
Top country — USA	32,830 (49.6%)	23,124 (41.9%)

Characteristic	Metformin (n=66,187)	Comparators (n=55,257)
2nd — Canada	8,546 (12.9%)	5,512 (10.0%)
3rd — France	4,559 (6.9%)	3,923 (7.1%)
Total cancer reports, n (%)	631 (0.95%)	315 (0.57%)

FAERS = FDA Adverse Event Reporting System. Age statistics restricted to year-coded entries (age_cod='YR') and validated range (1–110 years). Missing age reflects non-year-coded or absent entries.

Primary Analysis: Cancer-Specific Disproportionality

Table 2 and Figure 1 present cancer-specific disproportionality results. Significant signals were detected for five cancer types.

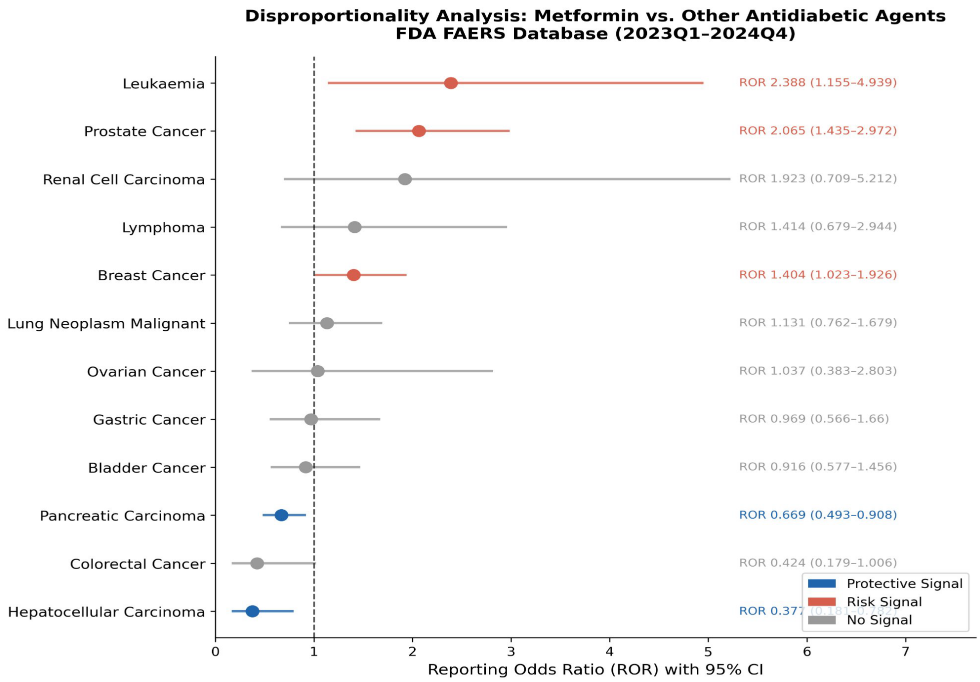

Figure 1. *Forest plot of cancer-specific Reporting Odds Ratios (ROR) with 95% confidence intervals for metformin versus all comparator antidiabetic agents. Blue circles = significant protective signals (ROR<1, CI excludes 1, p<0.05); Red circles = significant risk signals (ROR>1, CI excludes 1, p<0.05); Grey circles = no significant signal. Dashed vertical line at ROR=1 represents no difference. FDA FAERS, Q1 2023–Q4 2024.*

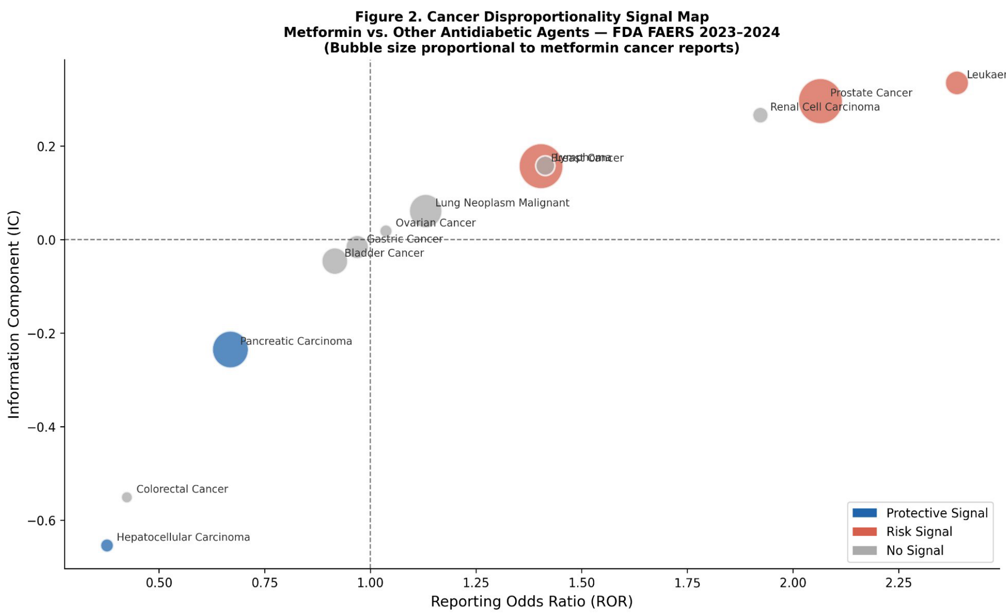

Figure 2. *Cancer disproportionality signal map. X-axis: Reporting Odds Ratio (ROR); Y-axis: Information Component (IC). Bubble size is proportional to the absolute number of metformin-associated cancer case reports. Upper-right quadrant = high ROR and positive IC (strongest risk signals); Lower-left quadrant = low ROR and negative IC (strongest protective signals). Dashed lines at ROR=1 and IC=0 represent null reference values.*

Protective Signals: Hepatocellular carcinoma demonstrated the strongest protective disproportionality signal (ROR 0.377, 95% CI 0.181–0.782, Chi^2=6.42, p=0.011), indicating that metformin was associated with approximately 62% lower cancer reporting odds compared to other antidiabetics. Pancreatic carcinoma also showed a statistically significant protective signal (ROR 0.669, 95% CI 0.493–0.908, Chi^2=6.32, p=0.012), representing approximately 33% lower reporting odds. Both findings are biologically consistent with metformin's documented AMPK-mediated suppression of hepatic and pancreatic tumor cell proliferation[11,14,33].

Risk Signals: Three cancer types met pre-specified signal criteria. Prostate cancer showed the most robust risk signal (ROR 2.065, 95% CI 1.435–2.972, Chi^2=15.31, p<0.001). Leukaemia was associated with significantly elevated reporting (ROR 2.388, 95% CI 1.155–4.939, Chi^2=5.16, p=0.023). Breast cancer also exceeded signal thresholds (ROR 1.404, 95% CI 1.023–1.926, Chi^2=4.15, p=0.042). No significant signals were detected for colorectal, bladder, gastric, ovarian, lung, renal cell carcinoma, or lymphoma.

Table 2. Cancer-Specific Disproportionality Results — Metformin vs. All Comparator Antidiabetic Agents

Cancer Type	Met (a)	Comp (c)	ROR	CI Lower	CI Upper	PRR	p-value	Signal
Hepatocellular Carcinoma	12	18	0.377	0.181	0.782	0.377	0.011	**Protective**
Pancreatic Carcinoma	90	76	0.669	0.493	0.908	0.670	0.012	**Protective**
Colorectal Cancer	9	12	0.424	0.179	1.006	0.424	0.075	—
Bladder Cancer	47	29	0.916	0.577	1.456	0.916	0.802	—
Gastric Cancer	36	21	0.969	0.566	1.660	0.969	1.000	—
Ovarian Cancer	11	6	1.037	0.383	2.803	1.037	1.000	—
Lung Neoplasm Malignant	74	37	1.131	0.762	1.679	1.131	0.608	—
Breast Cancer	134	54	1.404	1.023	1.926	1.403	0.042	**Risk**
Lymphoma	25	10	1.414	0.679	2.944	1.414	0.451	—
Renal Cell Carcinoma	17	5	1.923	0.709	5.212	1.922	0.278	—
Prostate Cancer	135	37	2.065	1.435	2.972	2.063	<0.001	**Risk**
Leukaemia	38	9	2.388	1.155	4.939	2.387	0.023	**Risk**

ROR = Reporting Odds Ratio; CI = Confidence Interval; PRR = Proportional Reporting Ratio; Met = Metformin; Comp = Comparator. Signal criteria: ROR>1 with lower CI>1 and p<0.05 (Risk); ROR<1 with upper CI<1 and p<0.05 (Protective). Minimum case threshold n≥5 applied.

Drug-Specific Comparisons (Table 3)

Metformin was significantly more favorable than sitagliptin (ROR 0.587, 95% CI 0.454–0.759, p<0.001) and empagliflozin (ROR 0.732, 95% CI 0.556–0.963, p=0.031) with regard to overall cancer reporting. Conversely, metformin was associated with significantly more cancer reports compared to insulin (ROR 1.201, 95% CI 1.021–1.413, p=0.030). No statistically significant differences were detected for semaglutide, liraglutide, glipizide, glimepiride, pioglitazone, dapagliflozin, or canagliflozin, though several showed non-significant trends. These drug-specific patterns are illustrated in Figure 4.

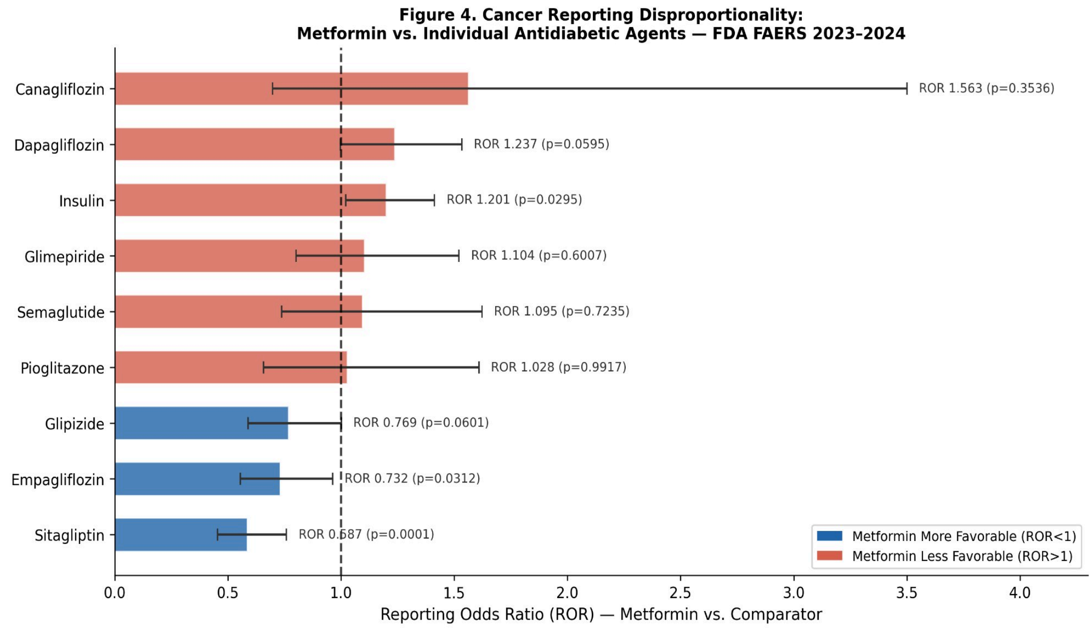

Figure 4. *Horizontal bar chart of cancer reporting disproportionality for metformin versus each antidiabetic comparator. Error bars represent 95% CI. Blue bars = metformin associated with less cancer reporting (ROR<1); Red bars = metformin associated with more cancer reporting (ROR>1). Dashed vertical line at ROR=1. Liraglutide excluded (insufficient cancer cases). P-values shown for each comparison.*

Table 3. Metformin vs. Individual Antidiabetic Agents — Overall Cancer Reporting Disproportionality

Comparator Drug	n (Cases)	Cancer (Comp)	ROR	CI Lower	CI Upper	PRR	p-value	Signal
Sitagliptin	4,029	65	0.587	0.454	0.759	0.591	<0.001	**Protective**
Empagliflozin	4,313	56	0.732	0.556	0.963	0.734	0.031	**Protective**
Glipizide	4,933	61	0.769	0.590	1.001	0.771	0.060	—
Pioglitazone	2,157	20	1.028	0.658	1.609	1.028	0.992	—
Semaglutide	2,983	26	1.095	0.738	1.623	1.094	0.724	—
Glimepiride	4,626	40	1.104	0.801	1.521	1.103	0.601	—
Dapagliflozin	12,431	96	1.237	0.997	1.534	1.235	0.060	—
Insulin	24,150	192	1.201	1.021	1.413	1.199	0.030	**Risk**
Canagliflozin	980	6	1.563	0.698	3.500	1.557	0.354	—

All comparisons use metformin (n=66,187; cancer reports=631) as the reference group. Signal criteria as per Table 2. Liraglutide excluded due to insufficient comparator cancer reports (n<5).

Quarterly Trend Analysis (Table 4)

Temporal analysis revealed variability in the ROR across the 8 study quarters (Table 4; Figure 3). A notable peak was observed in Q1 2024 (ROR 2.317, 95% CI 1.451–3.700, p<0.001), driven by a relative decrease in comparator group cancer reporting rate (0.32%) while metformin reporting remained stable (1.06%). Cancer reporting rates for the metformin group ranged from 0.73% to 1.09% across quarters compared to 0.32%–0.88% for comparators. Q4 2023 showed a non-significant trend toward protection (ROR 0.699, p=0.050).

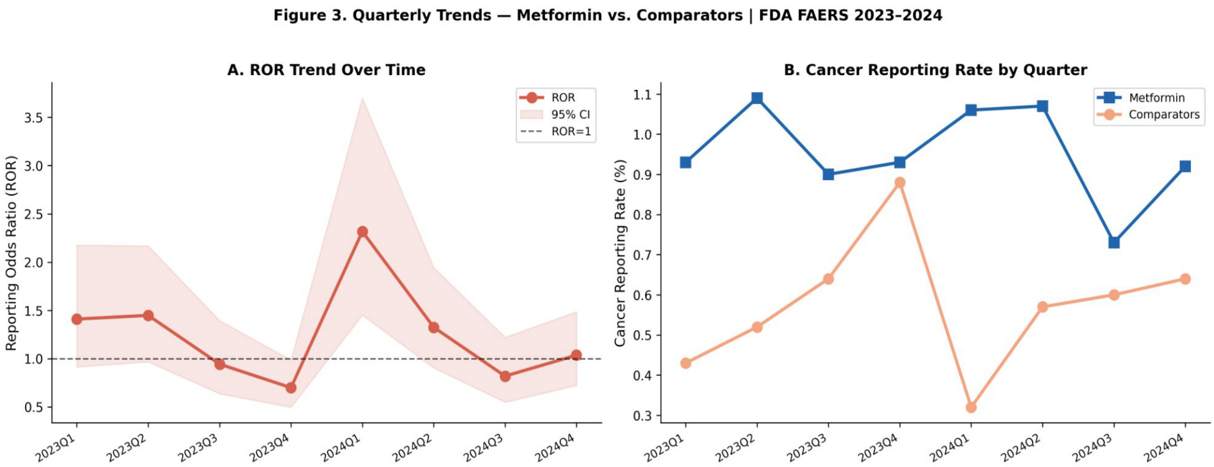

Figure 3. *Quarterly temporal trends in cancer disproportionality. Panel A: ROR trend over 8 study quarters (Q1 2023–Q4 2024) with 95% CI shading. Dashed line = ROR=1. Panel B: Cancer adverse event reporting rates (%) for metformin (blue) and comparator antidiabetics (orange) by quarter. Notable peak in 2024Q1 (ROR 2.317, p<0.001).*

Table 4. Quarterly Trend of Cancer Adverse Event Reporting — FDA FAERS, 2023–2024

Quarter	Met Cases	Cancer/Met	Rate (Met)	Comp Cases	Cancer/Comp	ROR (95% CI)	p-value
2023Q1	9,235	86	0.93%	6,341	27	1.410 (0.914–2.176)	0.145
2023Q2	8,470	92	1.09%	6,179	32	1.448 (0.967–2.168)	0.087
2023Q3	7,997	72	0.90%	6,057	39	0.943 (0.637–1.394)	0.845
2023Q4	8,404	78	0.93%	6,468	57	0.699 (0.496–0.986)	0.050
2024Q1	8,398	89	1.06%	6,959	22	**2.317 (1.451–3.700)**	<0.001
2024Q2	7,692	82	1.07%	6,862	39	1.325 (0.904–1.944)	0.176
2024Q3	7,955	58	0.73%	7,031	42	0.819 (0.549–1.220)	0.378
2024Q4	8,036	74	0.92%	7,846	50	1.036 (0.723–1.486)	0.919

Bold ROR = statistically significant (p<0.05). Rate = cancer reports as percentage of total drug reports in that quarter. ROR calculated using all-cancer composite outcome.

Discussion

This large-scale pharmacovigilance analysis of over 3.2 million FAERS adverse event reports identified distinct cancer-type-specific disproportionality patterns for metformin compared to other antidiabetic agents. The findings reveal a nuanced oncologic profile that differs substantially across cancer types and antidiabetic drug comparators, adding contemporary real-world evidence to a rapidly evolving field.

Hepatocellular and Pancreatic Carcinoma — Protective Signals

The strong protective disproportionality signal for HCC (ROR 0.377) represents the most compelling finding of this study and is consistent with the substantial literature on metformin's hepatoprotective and antitumor effects[34]. HCC predominantly arises in the setting of chronic liver disease, cirrhosis, and metabolic dysfunction-associated steatotic liver disease

(MASLD), conditions frequently comorbid with T2DM[35]. Mechanistically, metformin's preferential hepatic accumulation following portal absorption enables direct suppression of hepatic gluconeogenesis via AMPK activation and indirect reduction of hyperinsulinemia, both established promoters of HCC development[33,36]. Multiple meta-analyses have reported 3–50% reduced HCC risk in metformin-treated T2DM patients[11,37], and our pharmacovigilance findings corroborate these observations in a contemporary real-world reporting context.

The protective signal for pancreatic carcinoma (ROR 0.669) aligns with emerging evidence that metformin may inhibit pancreatic stellate cell activation and KRAS-driven oncogenic signaling[38]. This is clinically significant as T2DM is both a risk factor for and an early consequence of pancreatic ductal adenocarcinoma, creating a complex bidirectional relationship[39]. Notably, the AMPK-mTOR axis suppressed by metformin is hyperactivated in KRAS-mutant pancreatic cancer cells, providing a mechanistic rationale for the observed protective signal[40].

Prostate Cancer, Leukaemia, and Breast Cancer — Risk Signals

The elevated prostate cancer reporting signal (ROR 2.065) requires careful interpretation within the inherent limitations of pharmacovigilance methodology. Confounding by indication is a primary concern: men with T2DM receiving regular metformin prescriptions engage more frequently with the healthcare system, potentially increasing the probability of opportunistic PSA screening and prostate cancer diagnosis[41]. This surveillance bias, a well-documented phenomenon in pharmacovigilance studies involving common comorbidities, may substantially inflate the apparent reporting disproportionality [20]. Indeed, several large epidemiological studies and meta-analyses have reported either neutral or modestly protective effects of metformin on prostate cancer risk[42], suggesting that our pharmacovigilance signal may not reflect true biological risk.

The leukaemia signal (ROR 2.388), while statistically significant, was based on smaller absolute case numbers (n=38 metformin vs n=9 comparator) and carries wide confidence intervals (1.155–4.939), indicating statistical fragility. Preclinical evidence suggests metformin may actually exert anti-leukemic effects through AMPK-mediated inhibition of mTORC1 in acute lymphoblastic leukemia cells [43], further underscoring the need for caution in interpreting this signal. We recommend that this finding be treated as strictly hypothesis-generating pending replication in larger datasets.

The breast cancer signal (ROR 1.404) contrasts with the predominantly protective or neutral associations reported in epidemiological studies [44]. The IGF-1/insulin axis, modulated by metformin, plays complex roles in breast carcinogenesis that may differ by menopausal status, hormone receptor status, and metabolic phenotype[45]. The predominantly female demographic of the metformin group in our analysis (54.0%) and the inherent reporting biases of FAERS may contribute to this finding[19].

Drug-Specific Comparisons

The finding that metformin was associated with significantly lower overall cancer reporting compared to sitagliptin (ROR 0.587) is notable. DPP-4, the enzyme inhibited by sitagliptin, plays complex roles in tumor immunology and may promote certain malignancies by reducing immune surveillance through the truncation of stromal-derived factor 1-alpha (SDF-1α) and attenuating natural killer cell activity[46]. The protective comparison vs empagliflozin (ROR 0.732) may reflect differences in the patient populations prescribed each drug, as SGLT2 inhibitors are increasingly used in patients with established cardiovascular disease who may have higher baseline cancer risks[47].

The finding that insulin was associated with lower cancer reporting compared to metformin (ROR 1.201) appears counterintuitive given insulin's well-documented mitogenic effects via IGF-1R activation[48]. However, this likely reflects the channeling bias inherent to observational comparisons involving insulin, which is typically prescribed to patients with more advanced and longer-duration T2DM who may have different cancer risk profiles and healthcare engagement patterns.

These findings should be interpreted within the context of spontaneous reporting data and reflect reporting patterns rather than causal drug effects

Strengths and Limitations

This study has several notable strengths. It leverages a large, contemporary FAERS dataset comprising over 3.2 million adverse event reports, providing substantial statistical power for signal detection. The use of an active comparator design enhances internal validity by reducing confounding by indication, as all included drugs share the same therapeutic context for type 2 diabetes mellitus [21]. Cancer outcomes were pre-specified based on biological plausibility and prior literature, minimizing the risk of data-driven bias. In addition, the application of multiple complementary disproportionality metrics (ROR, PRR, IC, and chi-squared testing) strengthens the robustness of signal detection, while temporal trend analysis across eight quarters offers insight into the stability and evolution of reporting patterns over time. The use of standardized MedDRA terminology further supports consistency and reproducibility of outcome classification [23].

Despite these strengths, several important limitations inherent to FAERS must be carefully considered. First, FAERS is a passive spontaneous reporting system and is therefore subject to underreporting, selective reporting, duplicate submissions, and reporting bias, including stimulated reporting and the Weber effect[49]. Second, disproportionality analyses are particularly vulnerable to residual confounding, as key clinical variables such as cancer screening practices, diabetes severity, duration of drug exposure, concomitant medications, and comorbid conditions are not systematically captured and cannot be adequately controlled[50]. Third, the absence of denominator data prevents estimation of incidence rates or absolute risk, limiting interpretation to relative reporting frequencies rather than true risk quantification[20]. Fourth, temporal relationships between drug exposure and cancer onset cannot be reliably established due to incomplete or inconsistent reporting of treatment duration and latency periods. Fifth, variability in MedDRA coding and incomplete clinical detail may introduce outcome misclassification.

Accordingly, all findings from this analysis should be interpreted strictly as disproportionality signals reflecting reporting associations rather than causal relationships[51]. These results are best considered hypothesis-generating and should be validated in well-designed prospective studies and mechanistic investigations.

Conclusion

This large-scale pharmacovigilance analysis of over 3.2 million FAERS reports identified cancer-type-specific disproportionality signals for metformin compared with active comparator antidiabetic agents. The findings suggest a heterogeneous reporting profile, with reduced reporting signals for hepatocellular and pancreatic carcinoma and increased reporting signals for prostate cancer, leukaemia, and breast cancer.

Importantly, these results reflect reporting associations derived from spontaneous adverse event data and do not establish causal relationships. The observed signals may be influenced by reporting bias, residual confounding, differences in patient characteristics, and variability in healthcare utilization and cancer screening practices. In addition, the absence of denominator data in FAERS precludes estimation of incidence or absolute risk.

Overall, this study provides real-world pharmacovigilance evidence that is hypothesis-generating and contributes to the ongoing evaluation of metformin's oncologic profile. The findings should be interpreted with caution and require confirmation in well-designed prospective studies and mechanistic investigations.

Acknowledgements

Data Availability Statement: FAERS data are publicly available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The complete analysis code is available at https://github.com/kelyto30/metformin-cancer-faers (MIT License).

Code Availability: The complete analysis code is publicly available at https://github.com/kelyto30/metformin-cancer-faers (MIT License). All analyses were performed in Python 3.14 using open-source libraries: pandas, numpy, scipy, and matplotlib."

Ethics Approval: Not required. This study used publicly available, de-identified spontaneous adverse event reports and did not involve human subjects research.

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Protocol Registration: Study protocol registered at OSF.io before data analysis.

Author Contributions: Daniel Obinna Eke conceptualized the study, designed the methodology, performed data analysis, and drafted the original manuscript. Jessica Awingosit Ayamyiya contributed to study design, interpretation of results, and critical revision of the manuscript. Katabaazi Lillian Mirembe contributed to pharmacovigilance methodology and data interpretation. Anthony Kosisochukwu Anyabuoke contributed to data analysis, validation, and visualization. Jacqueline Azodoh contributed to the literature review and manuscript editing. Gloria Oluwabukunmi Oladapo contributed to supervision, critical review, and final approval of the manuscript. All authors read and approved the final version of the manuscript.

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AI Use Statement: Artificial intelligence tools (e.g., large language models) were used to assist with language refinement, grammar checking, and structural editing of the manuscript. All scientific content, data analysis, interpretation, and conclusions were developed and verified by the authors. The authors take full responsibility for the integrity and accuracy of the work.

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