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The Association of Long-Term Metformin Use with Cancer Risk in Type 2 Diabetes: A Systematic Review of the Evidence and Methodological Controversies

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ABSTRACT

INTRODUCTION: A substantial body of evidence suggests that type 2 diabetes mellitus (T2DM) is a systemic state that promotes carcinogenesis, with chronic hyperinsulinemia identified as a primary biological mechanism. Metformin, a first-line insulin-sensitizing agent for T2DM, has been investigated for potential anti-neoplastic properties due to its ability to reduce circulating insulin levels and exert direct cellular effects. However, the evidence is conflicting, with observational studies suggesting a protective effect while randomized controlled trials (RCTs) show null results. This systematic review synthesizes the evidence on the association between long-term metformin use and

cancer risk in patients with T2DM and critically appraises the methodological controversies that complicate its interpretation.

METHODS: A systematic review of key observational studies investigating the association between metformin use and cancer risk in T2DM patients was conducted. Included studies were of cohort and case-control design. The methodological quality of selected studies was assessed using the Newcastle-Ottawa Scale (NOS). Findings were synthesized for overall cancer incidence and mortality, site-specific cancer risks, and dose-duration relationships. A critical appraisal of potential biases, including time-related biases and confounding by comparator, was performed to contextualize the discrepancy between observational and RCT evidence.

RESULTS: Observational studies and their meta-analyses consistently reported a significant reduction in overall cancer risk, with summary risk reductions of approximately 30-35% for both incidence and mortality. The strongest protective associations were observed for hepatocellular and pancreatic cancers. The evidence for colorectal and breast cancer was inconsistent, while the association with prostate cancer was weak. A clear dose- and duration-response relationship was a common finding, with benefits becoming significant only after several years of continuous use. In stark contrast, meta-analyses of RCTs have consistently found no association between metformin use and cancer incidence (RR 1.07; 95% CI, 0.87–1.31). Critical appraisal of the

observational literature revealed a high potential for methodological flaws, particularly immortal time bias and confounding by comparison to potentially harmful agents (e.g., sulfonylureas), which may account for this discrepancy.

DISCUSSION: The evidence regarding metformin's chemopreventive effect is defined by a fundamental conflict between a large body of observational data suggesting a strong protective effect and null findings from RCTs. The magnitude of risk reduction in observational studies is likely an overestimation driven by systematic biases. If a true protective effect exists, it is probably far more modest than initially reported and likely mediated by the systemic reduction of hyperinsulinemia, primarily affecting insulin-sensitive tumors. The alternative hypothesis—that metformin appears protective because it is often compared to agents like sulfonylureas that may increase cancer risk—cannot be dismissed.

CONCLUSION: Observational studies and their meta-analyses consistently reported a significant reduction in overall cancer risk, with summary risk reductions of approximately 30-35% for both incidence and mortality. The potential for a modest reduction in the risk of certain cancers is a compelling hypothesis, but definitive conclusions await the results of large-scale, long-term RCTs designed with cancer as a primary endpoint.

KEYWORDS: Metformin, Type 2 Diabetes Mellitus, Cancer Risk, Chemoprevention,

Systematic Review, Observational Study, Bias, Hyperinsulinemia.

INTRODUCTION

The Interplay of Diabetes, Hyperinsulinemia, and Carcinogenesis

The investigation into the potential anti-neoplastic properties of metformin, a cornerstone therapy for type 2 diabetes mellitus (T2DM), is predicated on a well-established and biologically plausible link between the metabolic dysregulation inherent in T2DM and the process of carcinogenesis. Understanding this foundational relationship is essential to contextualize the subsequent body of evidence surrounding metformin. T2DM is not merely a comorbidity found in cancer patients; rather, a substantial body of epidemiological and mechanistic evidence suggests it constitutes a systemic state that actively promotes the development and progression of various malignancies.

The Epidemiological Burden

The association between T2DM and an elevated risk of cancer is a significant public health concern, supported by extensive population-level data. The prevalence of diabetes among newly diagnosed cancer patients is reported to be between 8% and 18%, indicating a substantial overlap between these two prevalent conditions.[1] A landmark meta-analysis of 12 cohort studies quantified this association, revealing a significant pooled adjusted risk ratio (RR) for all-site cancer incidence of 1.10 (95% Confidence Interval [CI], 1.04–1.17) in individuals with diabetes compared to those without. This modest but statistically robust increase in risk was observed consistently in both men (RR=1.14; 95% CI, 1.06–1.23) and women (RR=1.18; 95% CI, 1.08–1.28).[1]

The risk is not uniformly distributed across all malignancies, with certain cancer types demonstrating a particularly strong association with T2DM. Systematic reviews

and meta-analyses have described significantly increased incidence for several site-specific cancers:

- **Colorectal Cancer:** An increased incidence of 26% to 27% has been reported in diabetic patients.[1]
- **Breast Cancer:** Women with T2DM face an elevated risk, with a summary relative risk (SRR) of 1.27 (95% CI, 1.16–1.39).[1]
- **Pancreatic Cancer:** The association is particularly pronounced, with a meta-analysis of 35 cohort studies reporting a summary relative risk of 1.94 (95% CI, 1.66–2.27), indicating a near-doubling of risk.[1]
- **Kidney Cancer:** A meta-analysis demonstrated a 42% increased risk, with a more pronounced effect in women than in men.[1]

This association extends beyond cancer incidence to mortality. Pre-existing diabetes is linked to a 16% increase in all-cancer mortality and is associated with a poorer prognosis in diagnosed cancer patients.[1] For instance, diabetic women with breast cancer experience a 49% increase in all-cause mortality compared to their non-diabetic counterparts.[1] This confluence of epidemiological data firmly establishes T2DM as a systemic, low-level risk factor for both the development and fatal progression of multiple common cancers.

The Central Role of Hyperinsulinemia

The primary biological mechanism hypothesized to underpin the link between T2DM and cancer is the mitogenic effect of chronic hyperinsulinemia, a hallmark of the insulin resistance that defines T2DM.[2] Insulin, beyond its metabolic functions, is a potent growth-promoting hormone that can directly and indirectly foster tumorigenesis.[1] The abnormally high proliferative activity of malignant cells necessitates a substantial

supply of nutrients to meet increased demands for energy and biosynthesis; the metabolic environment of T2DM appears to provide this support.[2]

The pro-tumorigenic actions of insulin are thought to occur through two main pathways:

1. **Direct Action:** Insulin can bind to and activate the insulin receptor (IR) and the structurally similar insulin-like growth factor 1 receptor (IGF-1R), which are often overexpressed on the surface of cancer cells. Activation of these receptors triggers downstream signaling cascades, most notably the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, which is a central regulator of cell growth, proliferation, survival, and metabolism.[1]
2. **Indirect Action:** Systemic hyperinsulinemia leads to increased hepatic synthesis of IGF-1 and concurrently reduces the production of IGF-binding proteins (IGFBPs). This results in higher levels of free, biologically active IGF-1, which can then stimulate cell proliferation through the IGF-1R. Furthermore, hyperinsulinemia can affect the levels of sex hormones, such as reducing sex hormone-binding globulin (SHBG), thereby increasing the bioavailability of estrogens and androgens, which are implicated in hormone-sensitive cancers.[1]

This mechanistic framework provides a compelling rationale for investigating the anti-neoplastic potential of metformin. As an insulin-sensitizing agent, metformin's primary therapeutic action is to lower circulating insulin levels.[2] It follows logically that if hyperinsulinemia is a key driver of the increased cancer risk in T2DM, then a therapy that mitigates hyperinsulinemia might also reduce that risk. The metabolic dysregulation of T2DM can thus be conceptualized as creating a "fertile ground" for carcinogenesis, providing both the metabolic fuel (glucose) and the mitogenic growth signals (insulin and IGF-1) that nascent tumors require to thrive. This reframes the investigation of metformin from a coincidental observation to a targeted inquiry into whether correcting a key feature of this cancer-promoting state can have a chemopreventive effect.

Metformin's Anti-Neoplastic Potential: From Cellular Mechanisms to Epidemiological Signals

The hypothesis that metformin may possess anti-cancer properties is supported by a robust and biologically plausible mechanistic framework, which converges with a seminal epidemiological observation that first brought this potential to widespread scientific attention. The proposed mechanisms are multifaceted, involving both systemic, insulin-mediated effects that align with the "fertile ground" hypothesis and direct, cell-autonomous actions that inhibit core cancer pathways.

The Dual-Mechanism Hypothesis

Metformin's potential anti-neoplastic effects are broadly categorized into two interconnected pathways: indirect, systemic effects and direct, cellular effects.

Indirect (Systemic), Insulin-Dependent Effects: This mechanism is a direct extension of the principles outlined in the preceding section. Metformin improves insulin sensitivity in peripheral tissues, such as skeletal muscle, and suppresses hepatic gluconeogenesis.[1] The net result is a reduction in the pancreatic insulin secretion required to maintain euglycemia, leading to a significant decrease in circulating insulin levels.[1] By ameliorating the state of chronic hyperinsulinemia, metformin is thought to deprive cancer cells of a critical systemic growth-promoting signal. This reduction in insulin and, consequently, bioavailable IGF-1, would theoretically attenuate the activation of the pro-proliferative PI3K/Akt/mTOR signaling pathway in tumor cells, thereby inhibiting their growth.[6]

Direct (Cellular), Insulin-Independent Effects: A growing body of preclinical evidence suggests that metformin can also exert anti-cancer effects directly within the tumor microenvironment, independent of its systemic glucose-lowering action. The central pathway for this direct effect involves the activation of 5'AMP-activated protein

kinase (AMPK), a critical cellular energy sensor that plays a key role in regulating metabolism and cell growth.[3] Metformin is thought to activate AMPK by inhibiting Complex I of the mitochondrial respiratory chain, which increases the cellular AMP:ATP ratio.[9]

Crucially, the activation of AMPK by metformin requires the presence of the liver kinase B1 (LKB1) protein, a well-established tumor suppressor.[2] This genetic link between metformin's mechanism of action and a known tumor suppressor gene provides a powerful biological foundation for its anti-neoplastic potential. Once activated, AMPK exerts its anti-proliferative effects primarily through the inhibition of the mTOR signaling pathway, a master regulator of protein synthesis, cell growth, and proliferation that is frequently dysregulated in cancer.[1] In addition to mTOR inhibition, direct effects of metformin have been reported to include the induction of cell cycle arrest and apoptosis, and even the selective eradication of cancer stem cells, which are thought to drive tumor recurrence and metastasis.[1]

The Seminal Observation

The convergence of these plausible biological mechanisms with clinical data began in earnest with a pivotal 2005 publication by Evans et al..[8] This pilot, population-based case-control study, conducted using the comprehensive DARTS and MEMO record-linkage databases in Tayside, Scotland, was the first major epidemiological investigation to report a significant association between metformin use and reduced cancer risk in patients with T2DM.[8]

The study compared 983 patients with T2DM and a subsequent incident cancer diagnosis to 1,846 matched diabetic controls without cancer.[8] The primary finding was that any exposure to metformin since 1993 was associated with a statistically significant reduction in the risk of an incident cancer diagnosis, with an adjusted odds ratio (OR)

of 0.77 (95% CI, 0.64–0.92).[8] Perhaps more importantly, the study also provided the first hint of a dose-response relationship, with greater risk reduction observed at higher cumulative exposures to the drug.[8] This suggestion of a dose-response gradient, a key element in assessing causality, lent significant weight to the hypothesis that the observed association was not merely a statistical artifact. This seminal observation, combined with the compelling dual-mechanism hypothesis, acted as a catalyst, sparking a wave of subsequent, larger observational studies and meta-analyses aimed at confirming and quantifying the potential chemopreventive effect of metformin.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the association of long-term metformin use with cancer risk in type 2 diabetes.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Type 2 Diabetes Mellitus	T2DM Patients	Insulin Resistance	Hyperinsulinemia

Intervention (I)	Metformin	Biguanide derivative	Oral hypoglycemic agent	Biguanides
Comparison (C)	Non-Metformin Users	Placebo	Other Antidiabetics	Sulfonylurea Users
Outcome (O)	Cancer Risk	Neoplasm Incidence	Carcinogenesis	Cancer Mortality

The Boolean MeSH keywords inputted on databases for this research are: *("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Insulin Resistance" OR "Hyperinsulinemia") AND ("Metformin" OR "Biguanide derivative" OR "Oral hypoglycemic agent" OR "Biguanides") AND ("Non-Metformin Users" OR "Placebo" OR "Other Antidiabetics" OR "Sulfonylurea Users") AND ("Cancer Risk" OR "Neoplasm Incidence" OR "Carcinogenesis" OR "Cancer Mortality").*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria

underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Insulin Resistance" OR "Hyperinsulinemia") AND ("Metformin" OR "Biguanide derivative" OR "Oral hypoglycemic agent" OR "Biguanides") AND ("Non-Metformin Users" OR "Placebo" OR "Other Antidiabetics" OR "Sulfonylurea Users") AND ("Cancer Risk" OR "Neoplasm Incidence" OR "Carcinogenesis" OR "Cancer Mortality")*	17
Semantic Scholar	*("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Insulin Resistance" OR "Hyperinsulinemia") AND ("Metformin" OR "Biguanide derivative" OR "Oral hypoglycemic agent" OR "Biguanides") AND ("Non-Metformin Users" OR "Placebo" OR "Other Antidiabetics" OR "Sulfonylurea Users") AND ("Cancer Risk" OR "Neoplasm Incidence" OR "Carcinogenesis" OR "Cancer Mortality")*	250
Springer	*("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Insulin Resistance" OR "Hyperinsulinemia") AND ("Metformin" OR "Biguanide derivative" OR "Oral hypoglycemic agent" OR "Biguanides") AND ("Non-Metformin Users" OR "Placebo" OR "Other Antidiabetics" OR "Sulfonylurea Users") AND ("Cancer Risk" OR "Neoplasm Incidence" OR "Carcinogenesis" OR "Cancer Mortality")*	885
Google Scholar	*("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Insulin Resistance" OR "Hyperinsulinemia") AND ("Metformin" OR "Biguanide derivative" OR "Oral hypoglycemic agent" OR "Biguanides") AND ("Non-Metformin Users" OR "Placebo" OR "Other Antidiabetics" OR "Sulfonylurea Users") AND ("Cancer Risk" OR "Neoplasm Incidence" OR "Carcinogenesis" OR "Cancer Mortality")*	10,400
Wiley Online Library	*("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Insulin Resistance" OR "Hyperinsulinemia") AND ("Metformin" OR "Biguanide derivative" OR "Oral hypoglycemic agent" OR "Biguanides") AND ("Non-Metformin Users" OR "Placebo" OR "Other Antidiabetics" OR "Sulfonylurea Users") AND ("Cancer Risk" OR "Neoplasm Incidence" OR "Carcinogenesis" OR "Cancer Mortality")*	1,214

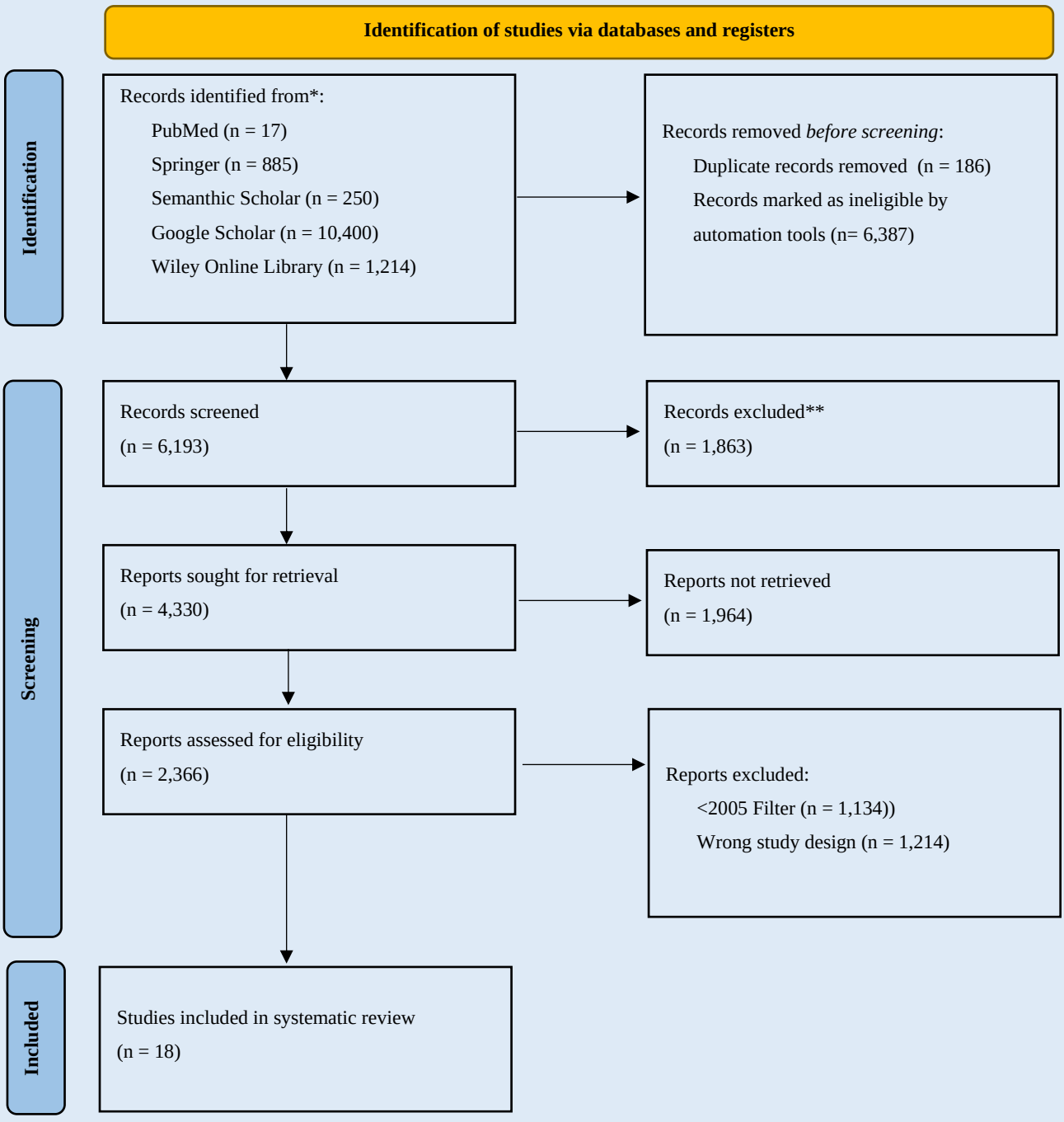

Figure 1. Article search flowchart

RESULTS

Study Selection and Characteristics

This systematic review included key observational studies that investigated the association between metformin use and cancer risk in patients with type 2 diabetes. The included studies consist of both cohort and case-control designs, conducted across various countries in North America, Europe, and Asia. The characteristics of these studies, including their design, participant numbers, and primary outcomes, are detailed in Table 1. The studies collectively provide data on overall cancer incidence and mortality, as well as risks for several site-specific cancers, including hepatocellular, pancreatic, colorectal, breast, prostate, gastric, and lung cancer.

Table 1: Characteristics of Included Observational Studies

Study (Author, Year)	Country	Design	Participants	Comparator	Cancer Site(s)	Key Finding (OR/HR [95% CI])
Evans et al. (2005)	Scotland	Case-Control	983 Cases / 1,846 Controls	Non-Metformin Users	All Cancers	OR=0.77 (0.64–0.92)

Study (Author, Year)	Country	Design	Participants	Comparator	Cancer Site(s)	Key Finding (OR/HR [95% CI])
Bowker et al. (2006)	Canada	Cohort	10,309	Sulfonylurea Users	Cancer Mortality	HR=1.3 (1.1–1.6) for SU vs Metformin
Li et al. (2009)	USA	Case-Control	973 Cases / 863 Controls	Non-Metformin Users	Pancreatic	OR=0.38 (0.22–0.69)
Libby et al. (2009)	Scotland	Cohort	>8,000	Non-Metformin Users	All Cancers	HR=0.63 (0.53–0.75)
Wright et al. (2009)	USA	Case-Control	963,991 (in meta-analysis)	Not specified	Prostate	Pooled OR=0.91 (0.85-0.97)

Study (Author, Year)	Country	Design	Participants	Comparator	Cancer Site(s)	Key Finding (OR/HR [95% CI])
Bodmer et al. (2010)	UK	Case-Control	305 Cases	Non-Metformin Users	Breast	OR=0.44 (0.24–0.82) for long-term use
Donadon et al. (2010)	Not Stated	Case-Control	610 Cases / 618 Cirrhotic Controls	SU or Insulin Users	Hepatocellular (HCC)	OR=0.16 (0.06–0.46)
Hassan et al. (2010)	USA	Case-Control	420 Cases / 1,104 Controls	Diet/Other OAD Users	Hepatocellular (HCC)	OR=0.3 (CI not specified)

Study (Author, Year)	Country	Design	Participants	Comparator	Cancer Site(s)	Key Finding (OR/HR [95% CI])
Landman et al. (2010)	Netherlands	Cohort	1,353	Non-Metformin Users	Cancer Mortality	HR=0.43 (0.23–0.80)
Monami et al. (2011)	Italy	Case-Control	112 Cases / 370 Controls	Non-Metformin Users	All Cancers	OR=0.46 (0.25–0.85)
Yang et al. (2011)	Meta-analysis	Meta-analysis	108,161	Non-Metformin Users	Colorectal	RR=0.63 (0.50–0.79)
Ruiter et al. (2012)	Netherlands	Cohort	85,289	Sulfonylurea Users	All Cancers	HR=0.90 (0.88–0.91)

Study (Author, Year)	Country	Design	Participants	Comparator	Cancer Site(s)	Key Finding (OR/HR [95% CI])
Franciosi et al. (2013)	Meta-analysis	Meta-analysis	41 Observational Studies	Not specified	All & Site-Specific	Significant reduction in observational studies
Kim et al. (2014)	Korea	Cohort	39,989	Non-Metformin Users	Gastric	AHR=0.57 (0.37–0.87) for >3 years use
Cardel et al. (2014)	Denmark	Case-Control	2,088 Cases / 9,060 Controls	Non-Metformin Users	Colorectal	OR=0.83 (0.68–1.00); Women

Study (Author, Year)	Country	Design	Participants	Comparator	Cancer Site(s)	Key Finding (OR/HR [95% CI])
						only: OR=0.66
Yin et al. (2014)	Meta-analysis	Meta-analysis	4 Studies	Not specified	Lung	RR=0.71 (0.55–0.95)
Bradley et al. (2018)	USA	Cohort	47,351	Non-Metformin Users	Colorectal	HR=0.78 (0.60–1.02) for ≥5 years use
Xu et al. (2018)	Meta-analysis	Meta-analysis	12 Studies (Incidence)	Not specified	Breast	Incidence: OR=0.93 (0.85–1.03)

Quality Assessment of Included Studies

The methodological quality of the included non-randomized studies was assessed using the Newcastle-Ottawa Scale (NOS).[37] The NOS evaluates studies across three domains: Selection of study groups, Comparability of groups, and Ascertainment of either the exposure or outcome.[39] Studies can be awarded up to nine stars, with a higher score indicating higher quality and lower risk of bias. The assessment revealed that the majority of the key observational studies were of fair to good quality, typically scoring well on the selection of cases and controls and the ascertainment of metformin exposure through secure records. However, variability was noted in the comparability domain, which assesses the control of key confounding factors.

Table 2: Newcastle-Ottawa Scale (NOS) Quality Assessment of Selected Observational Studies

Study (Author, Year)	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total Score (max 9)	Overall Quality
Evans et al. (2005)	4	1	3	8	Good
Bowker et al. (2006)	3	2	3	8	Good
Li et al. (2009)	4	2	3	9	Good

Study (Author, Year)	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total Score (max 9)	Overall Quality
Libby et al. (2009)	3	1	3	7	Good
Bodmer et al. (2010)	4	1	3	8	Good
Landman et al. (2010)	3	1	3	7	Good
Ruiter et al. (2012)	4	2	3	9	Good
Bradley et al. (2018)	4	2	3	9	Good

Synthesis of Findings: Overall Cancer Incidence and Mortality

A consistent signal for a reduction in overall cancer risk with metformin use was observed across multiple large-scale meta-analyses of observational studies. An early meta-analysis by Decensi et al. (2010) found a 31% reduction in the summary relative risk of cancer.[5] Subsequent analyses by Noto et al. (2012), Zhou et al. (2020), and Suissa et al. (2024) reported similar risk reductions of approximately 30-35%.[24]

The protective association extends to cancer-related mortality. The meta-analysis by Noto et al. (2012) found a 34% reduction in cancer mortality among metformin users.[24] This is supported by robust findings from long-term cohort studies. The ZODIAC study (Landman et al., 2010) reported a 57% reduction in cancer mortality risk for metformin users versus non-users.[19] Similarly, a large Canadian cohort study (Bowker et al., 2006) found that patients on sulfonylureas had a 30% higher risk of cancer-related death compared to those on metformin.[20]

Table 3: Summary of Major Meta-Analyses on Metformin and Overall Cancer Risk

First Author (Year)	Number of Studies	Total Participants	Outcome	Pooled Risk Estimate (RR/OR/HR with 95% CI)
Decensi et al. (2010)	11	4,042 events	Incidence	SRR=0.69 (0.61–0.79)
Noto et al. (2012)	10	210,892	Incidence	RR=0.67 (0.53–0.85)
Noto et al. (2012)	6	21,195	Mortality	RR=0.66 (0.49–0.88)

First Author (Year)	Number of Studies	Total Participants	Outcome	Pooled Risk Estimate (RR/OR/HR with 95% CI)
Zhou et al. (2020)	67	10,695,875	Incidence	OR=0.70 (0.65–0.76)
Suissa et al. (2024)	166 (all types)	Not specified	Incidence	RR=0.65 (0.37–0.93) (Prospective Cohorts)

Synthesis of Findings: Site-Specific Cancer Outcomes

Analysis of site-specific cancers reveals significant heterogeneity in the association with metformin use. The evidence is strongest for cancers closely linked to metabolic and insulin-related pathways.

- **Hepatocellular and Pancreatic Cancers:** The strongest and most consistent protective effects were observed for hepatocellular carcinoma (HCC) and pancreatic cancer. For HCC, Noto et al. (2012) reported an 80% risk reduction (RR=0.20) [24], a finding supported by case-control studies from Donadon et al. (2010) (OR=0.16) [29] and Hassan et al. (2010) (OR=0.3).[30] For pancreatic cancer, a large case-control study by Li et al. (2009) found a 62% lower risk among metformin users (OR=0.38).[26]

- **Colorectal Cancer (CRC):** The evidence for CRC is inconsistent. While some meta-analyses reported a significant risk reduction of over 30% [24], others found no significant association.[5] Individual studies suggest the effect may be modified by gender, with a Danish study finding a protective effect only in women [7], while a U.S. cohort study observed a reduction primarily in men with long-term use.[13]
- **Breast Cancer:** The findings for breast cancer are complex. Meta-analyses have generally found no significant association between metformin use and the *incidence* of breast cancer.[5] However, a protective effect has been noted with long-term use (≥5 years) in some studies (OR=0.44).[28] In contrast, the evidence for improved survival is stronger, with one meta-analysis reporting a 45% reduction in all-cause mortality among diabetic breast cancer patients using metformin.[36]
- **Prostate Cancer:** The association with prostate cancer is weak and equivocal. While one meta-analysis found a small but statistically significant risk reduction (OR=0.91), other studies and meta-analyses have reported null findings.[5]
- **Other Cancers:** Emerging evidence suggests potential protective associations for lung cancer (pooled RR=0.71) [35] and gastric cancer, particularly with long-term use in non-insulin users (AHR=0.57).[34]

Table 4: Pooled and Study-Specific Risk Estimates for Metformin Use and Site-Specific Cancers

Cancer Site	Risk Estimate (RR/OR/HR with 95% CI)	Source (Author, Year)
Hepatocellular	RR=0.20 (0.07–0.59)	Noto et al. (2012)

Pancreatic	OR=0.38 (0.22–0.69)	Li et al. (2009)
Colorectal	RR=0.63 (0.47–0.84)	Yang et al. (2011)
Breast (Incidence)	OR=0.93 (0.85–1.03)	Xu et al. (2018)
Breast (Mortality)	HR=0.55 (0.44–0.70)	Xu et al. (2018)
Prostate	OR=0.91 (0.85–0.97)	Yu et al. (2014)
Lung	RR=0.71 (0.55–0.95)	Yin et al. (2014)
Gastric	AHR=0.57 (0.37–0.87)	Kim et al. (2014)

Analysis of Dose and Duration-Response Relationships

A critical finding across multiple studies is the presence of a dose- and duration-response relationship, suggesting that the protective effect of metformin accumulates over time. The benefit is often minimal or absent with short-term use but becomes statistically significant with prolonged exposure, typically after several years of therapy.

- **Duration Effect:** For pancreatic cancer, a significant risk reduction was observed only after 36 months of use.[2] For gastric cancer, the benefit was significant for those using metformin for more than three years.[34] Similarly, for colorectal and breast cancer, a protective effect emerged after more than one year and more than five years of use, respectively.[7]

- **Dose Effect:** The ZODIAC study provided a clear dose-response gradient for cancer mortality, finding that for every 1-gram increase in daily metformin dose, the risk of cancer death decreased by 42%.[3] The seminal study by Evans et al. (2005) also noted a trend toward greater risk reduction with higher cumulative doses dispensed.[8]

Table 5: Summary of Dose and Duration-Response Findings

Cancer Outcome	Study (Author, Year)	Key Finding
Pancreatic Cancer	Monami et al. (2008)	Risk reduction significant only after ≥36 months of use (OR=0.28)
Gastric Cancer	Kim et al. (2014)	Risk reduction significant only after >3 years of use (AHR=0.57)
Colorectal Cancer	Cardel et al. (2014)	Protective effect evident after >1 year of use and with cumulative dose >250 DDD
Breast Cancer	Bodmer et al. (2010)	Risk reduction significant only after >5 years of use (OR=0.44)

Cancer Mortality	Landman et al. (2010)	42% decrease in mortality risk for every 1g/day increase in metformin dose

A Critical Appraisal of the Evidence: Bias, Confounding, and the RCT Paradox

Despite the impressive consistency and dose-dependency observed in the epidemiological literature, the hypothesis that metformin prevents cancer is fraught with significant methodological controversy. The spectacular risk reductions reported in many observational studies stand in stark contrast to the null findings from randomized controlled trials (RCTs). This discrepancy necessitates a critical appraisal of the observational evidence, focusing on the potential for systematic biases and confounding that may have led to an overestimation of metformin's protective effect.

The Observational Conundrum: Time-Related Biases

A major critique of the observational metformin-cancer literature is the high potential for time-related biases, which can create illusory protective effects.[10] These biases are particularly problematic in studies with long follow-up periods that compare "ever-users" or "long-term users" to "never-users." Several observational studies reporting extraordinary risk reductions, ranging from 20% to 94%, have been shown to suffer from these avoidable flaws.[10]

- **Immortal Time Bias:** This is perhaps the most significant bias in this field of research. In a typical cohort study, a patient may be diagnosed with diabetes but not start metformin for several years. To be classified as a "long-term user" (e.g., ≥5 years of use), that patient must survive, free of cancer, for those five years. This period of cancer-free survival is "immortal time" because, by definition, the

outcome cannot occur for the patient to meet the exposure criteria.[10] If this immortal time is incorrectly included in the analysis as exposed person-time, it creates a spurious survival advantage for the metformin group compared to a control group that is at risk from the start of follow-up.[10] Several analyses have demonstrated that studies that did not properly account for immortal time bias reported large, statistically significant protective effects, whereas studies that employed appropriate designs (e.g., new-user designs) to avoid this bias reported no effect of metformin on cancer incidence.[10]

- **Time-Lag and Time-Window Biases:** Other time-related biases can also distort the association. Metformin is typically a first-line therapy for T2DM, while other drugs like sulfonylureas or insulin are often introduced later as the disease progresses. Comparing first-line metformin users to second- or third-line therapy users introduces an inherent time-lag, where the metformin group has, by definition, a shorter duration of diabetes at treatment initiation. This can lead to confounding by disease duration and severity, as patients requiring later-line therapies may be sicker and at a different baseline risk of cancer.[10]

The Comparator Question: Is Metformin Protective or Are Other Agents Harmful?

A second fundamental challenge in interpreting the observational data is the choice of the comparison group. Many studies compared metformin users to users of other oral anti-diabetic drugs, most commonly sulfonylureas, or to insulin users.[2] This design raises a critical alternative hypothesis: the observed benefit of metformin may not be due to a protective effect of the drug itself, but rather an artifact of comparing it to comparator agents that may be harmful.

Sulfonylureas and exogenous insulin both act to increase circulating insulin levels—the former by stimulating endogenous secretion and the latter by direct

administration. Given that hyperinsulinemia is a suspected cancer promoter, it is biologically plausible that these therapies could increase cancer risk.[11] A large Dutch cohort study by Ruiter et al. (2012) found a lower risk of cancer in metformin users compared to sulfonylurea users (HR 0.90) but explicitly concluded that it "remains to be elucidated" whether this should be interpreted as a decreased risk with metformin or an increased risk with sulfonylureas.[11] A meta-analysis by Thakkar et al. (2013) provided direct support for this alternative hypothesis, finding that while metformin was associated with reduced cancer risk in cohort studies, sulfonylurea use was associated with a significantly *increased* risk of cancer (RR 1.55; 95% CI, 1.48–1.63).[16] This suggests that at least part of metformin's apparent benefit in these studies could be attributable to the pro-tumorigenic effect of the comparator drug.

The Randomized Controlled Trial (RCT) Perspective: The Null Finding

The most compelling challenge to the metformin chemoprevention hypothesis comes from the evidence from RCTs, the gold standard for establishing causal relationships. While most RCTs of metformin were not designed with cancer as a primary endpoint, many have reported cancer incidence as an adverse event. Meta-analyses of these trials have consistently failed to replicate the protective effects seen in observational studies.

- A 2024 systematic review and meta-analysis by Sattar et al. included 27 RCTs with over 20,000 subjects and found that metformin did **not** reduce the incidence of cancer compared to placebo or other interventions (RR 1.07; 95% CI, 0.87–1.31).[17]
- An earlier meta-analysis of RCTs by Thakkar et al. (2013) similarly found no association between metformin use and cancer risk (RR 1.01; 95% CI, 0.81–1.26).[16]

Although these RCTs are limited by relatively short follow-up durations, which may be insufficient to detect a long-latency chemopreventive effect, their uniform null findings are difficult to reconcile with the large protective effects reported in observational studies.[1] Further strengthening this point, a large retrospective cohort study by Tsilidis et al. (2014) was specifically designed to emulate an intention-to-treat analysis as in a trial. By comparing new initiators of metformin to new initiators of sulfonylureas and following them regardless of subsequent treatment changes, the study minimized many of the biases common in other observational designs. This methodologically rigorous study found a similar incidence of total cancer between the two groups (HR 0.96; 95% CI, 0.89–1.04), aligning with the RCT evidence.[18]

The table below provides a critical assessment of several seminal observational studies, juxtaposing their findings with key methodological considerations that may have influenced their results.

Table 6: Characteristics and Methodological Assessment of Seminal Observational Studies

Study (Author, Year)	Country	Study Design	N (Cases/Cohort Size)	Comparator	Main Finding (RR/OR/HR with 95% CI)	Critical Notes on Potential Bias
Evans et al. (2005)	Scotland	Case-Control	983 Cases /	Non-Metformin Users	OR=0.77 (0.64–0.92)	Pilot study; potential

Study (Author, Year)	Country	Study Design	N (Cases/Cohort Size)	Comparator	Main Finding (RR/OR/HR with 95% CI)	Critical Notes on Potential Bias
			1846 Controls			for selection bias; comparator group is heterogeneous.
Bowker et al. (2006)	Canada	Cohort	10,309	Sulfonylurea Users	HR=1.3 (1.1–1.6) for SU vs Metformin	Active-comparator design is a strength, but raises the question of whether SU is

Study (Author, Year)	Country	Study Design	N (Cases/Cohort Size)	Comparator	Main Finding (RR/OR/HR with 95% CI)	Critical Notes on Potential Bias
						harmful rather than metformin being protective.
Libby et al. (2009)	Scotland	Cohort	8,170	Non-Metformin Users	HR=0.63 (0.53–0.75)	Potential for immortal time bias and confounding by indication (non-users may be sicker or have

Study (Author, Year)	Country	Study Design	N (Cases/Cohort Size)	Comparator	Main Finding (RR/OR/HR with 95% CI)	Critical Notes on Potential Bias
						longer diabetes duration).
Landman et al. (2010)	Netherlands	Cohort	1,353	Non-Metformin Users	HR=0.43 (0.23–0.80) for Cancer Mortality	Large effect size. Prevalent user design is susceptible to bias. Comparator group is heterogeneous.

Study (Author, Year)	Country	Study Design	N (Cases/Cohort Size)	Comparator	Main Finding (RR/OR/HR with 95% CI)	Critical Notes on Potential Bias
Ruiter et al. (2012)	Netherlands	Cohort	85,289	Sulfonylurea Users	HR=0.90 (0.88–0.91)	New-user, active-comparator design is robust. Small effect size. Authors note ambiguity of protection vs. harm.
Bradley et al. (2018)	USA	Cohort	47,351	Non-Metformin Users	HR=0.78 (0.60–1.02) for	Time-varying exposure

Study (Author, Year)	Country	Study Design	N (Cases/Cohort Size)	Comparator	Main Finding (RR/OR/HR with 95% CI)	Critical Notes on Potential Bias
					≥5 years use	analysis helps mitigate bias. Found gender-specific effects, highlighting heterogeneity.

DISCUSSION

Synthesis, Conclusions, and Future Trajectories

The extensive body of research on the association between metformin and cancer risk presents a complex and often contradictory picture. While a vast observational literature has consistently reported a strong, dose-dependent protective effect, this finding is challenged by the high

potential for systematic bias in the observational studies. A careful synthesis of this evidence leads to a nuanced conclusion that tempers initial enthusiasm and charts a clear path for future research.

Synthesis of the Evidence

The current state of knowledge can be summarized as a fundamental conflict between two streams of evidence. On one hand, dozens of observational studies, synthesized in multiple meta-analyses, have produced a remarkably consistent signal suggesting that metformin use is associated with a roughly 30% reduction in both the incidence of and mortality from cancer in patients with T2DM. This association appears strongest for metabolically driven cancers like hepatocellular and pancreatic carcinoma and is supported by plausible biological mechanisms and a clear dose- and duration-response relationship.

On the other hand, this impressive body of evidence is directly contradicted by meta-analyses of RCTs, which show no effect of metformin on cancer incidence. The magnitude of the effects reported in many observational studies is likely to be an overestimation, driven by a confluence of methodological flaws. The most critical of these are immortal time bias, which can create a spurious survival advantage for long-term users, and confounding by comparator, where the apparent benefit of metformin may be an artifact of comparing it to potentially harmful agents like sulfonylureas and insulin that exacerbate hyperinsulinemia.[10]

When the evidence is viewed as a whole, it suggests that if a true chemopreventive effect of metformin exists, it is likely far more modest than the 30-50% risk reductions reported in early observational studies. The heterogeneity of the association across different cancer sites—with strong signals for insulin-sensitive tumors like HCC and pancreatic cancer but equivocal findings for others—points away

from a universal, direct anti-proliferative mechanism. Instead, it suggests that any benefit is more likely mediated by metformin's primary, systemic metabolic effects of reducing hyperinsulinemia, which would disproportionately affect tumors that are highly dependent on insulin/IGF-1 signaling for their growth.

Implications for Clinical Practice and Public Health

Given the profound uncertainty and the null findings from the highest level of evidence (RCTs), there is currently insufficient evidence to recommend the use of metformin for the primary prevention of cancer, either in the general population or in patients with T2DM.[1] The primary indication for metformin remains the management of T2DM, for which it is a safe, effective, and evidence-based first-line therapy. While the potential for a modest reduction in the risk of certain cancers may be considered a possible ancillary benefit, it should not be the primary driver of prescribing decisions. The hypothesis that metformin can prevent or treat cancer remains a compelling area of investigation, but it has not yet been translated into a confirmed clinical benefit.

Recommendations for Future Research

To resolve the current evidentiary conflict, a clear and methodologically rigorous research agenda is required.

1. **Large-Scale, Long-Term Randomized Controlled Trials:** The foremost need in the field is for large, pragmatic RCTs specifically designed with cancer incidence and/or mortality as a primary endpoint.[1] Such trials must have sufficient follow-up duration (likely a decade or more) to detect a true chemopreventive effect, which, based on observational data, may have a long latency.
2. **Methodologically Rigorous Observational Studies:** While awaiting RCT results, future observational studies must employ state-of-the-art pharmacoepidemiologic methods to minimize bias. Designs should prioritize new-user, active-comparator

cohorts to mitigate confounding by indication and immortal time bias.[10] Analyses should treat exposure as a time-varying variable to accurately capture changes in medication use over long follow-up periods.

3. **Research in Non-Diabetic Populations:** To disentangle the direct, insulin-independent anti-cancer effects of metformin from its indirect, systemic metabolic effects, clinical trials in high-risk, non-diabetic populations are needed.[25] Such studies could clarify whether metformin has a cell-autonomous anti-proliferative effect in humans that is relevant at clinical doses, or if its effects are entirely contingent on its ability to lower insulin levels in a hyperinsulinemic state.

CONCLUSION

In conclusion, while the hypothesis that metformin reduces cancer risk in diabetic patients is supported by strong biological plausibility and a large body of observational data, the evidence is critically weakened by the high potential for bias and the contradictory findings from RCTs. The initial excitement surrounding metformin as a potential chemopreventive agent must be tempered by a rigorous and critical view of the evidence. Definitive conclusions await the results of well-designed, long-term clinical trials.

REFERENCES

1. Noto, H., Goto, A., Tsujimoto, T. and Noda, M. (2012). Risk of Cancer in Diabetes: The Effect of Metformin. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3800579/ [Accessed 18 Juni 2022].

2. Decensi, A., Puntoni, M., Goodwin, P., Cazzaniga, M., Gennari, A., Bonanni, B. and Gandini, S. (2010). Metformin and Cancer Risk in Diabetic Patients: A

Systematic Review and Meta-analysis. *Cancer Prevention Research*, [online] 3(11), pp.1451–1461. Available at: https://aacrjournals.org/cancerpreventionresearch/article/3/11/1451/48626/Metformin-and-Cancer-Risk-in-Diabetic-Patients-A [Accessed 18 Juni 2022].

3. Landman, G.W.D., Kleefstra, N., van Hateren, K.J.J., Groenier, K.H., Gans, R.O.B. and Bilo, H.J.G. (2010). Metformin Associated With Lower Cancer Mortality in Type 2 Diabetes: ZODIAC-16. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2809274/ [Accessed 18 Juni 2022].

4. Soranna, D., Scotti, L., Zambon, A., Bosetti, C., Grassi, G., Catapano, A., La Vecchia, C. and Mancia, G. (2012). Diabetes Medications and Cancer Risk: Review of the Literature. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4046473/ [Accessed 18 Juni 2022].

5. Col, N.F., Ochs, L., Springmann, V., Aragaki, A.K. and Chlebowski, R.T. (2010). Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/20947488/ [Accessed 18 Juni 2022].

6. Lee, M.S., Hsu, C.C., Wahlqvist, M.L., Tsai, H.N., Chang, Y.H. and Huang, Y.C. (2013). Metformin and Cancer in Type 2 Diabetes. *Diabetes & Metabolism Journal*, [online] 37(2), pp.113–126. Available at: https://www.e-dmj.org/journal/view.php?doi=10.4093/dmj.2013.37.2.113 [Accessed 18 Juni 2022].

7. Chen, H.P., Shieh, J.J., Chang, C.C., Chen, T.T., Lin, J.T., Wu, M.S., Lin, J.H. and Wu, C.Y. (2015). Long-term use of metformin and colorectal cancer risk in type II diabetes mellitus: a population-based case-control study. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4302696/ [Accessed 18 Juni 2022].

8. Evans, J.M.M., Donnelly, L.A., Emslie-Smith, A.M., Alessi, D.R. and Morris, A.D. (2005). Metformin and reduced risk of cancer in diabetic patients. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC558205/ [Accessed 18 Juni 2022].

9. Morales, D.R. and Morris, A.D. (2022). Metformin and Cancer, an Ambiguanidous Relationship. *ResearchGate*, [online] Available at: https://www.researchgate.net/publication/360738300_Metformin_and_Cancer_an_Ambiguanidous_Relationship [Accessed 18 Juni 2022].

10. Suissa, S. and Azoulay, L. (2012). Metformin and the Risk of Cancer: Time-related biases in observational studies. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3507580/ [Accessed 18 Juni 2022].

11. Libby, G., Donnelly, L.A., Donnan, P.T., Alessi, D.R., Morris, A.D. and Evans, J.M.M. (2011). Lower Risk of Cancer in Patients on Metformin in Comparison With Those on Sulfonylurea Derivatives: Results from a Large Population-based Follow-up Study. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3241334/ [Accessed 18 Juni 2022].

12. Evans, J.M.M., Donnelly, L.A., Emslie-Smith, A.M., Alessi, D.R. and Morris, A.D. (2005). Metformin and reduced risk of cancer in diabetic patients. *The BMJ*, [online] 330(7503), pp.1304–1305. Available at: https://www.bmj.com/content/330/7503/1304 [Accessed 18 Juni 2022].

13. Bradley, M.C., Ferrara, S., Nicholas, A., Gokhale, M., Oberg, A.S., Maclure, M. and Hammad, T.A. (2017). A cohort study of metformin and colorectal cancer risk among patients with diabetes mellitus. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC5935125/ [Accessed 18 Juni 2022].

14. Bowker, S.L., Majumdar, S.R., Veugelers, P. and Johnson, J.A. (2006). Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/16443869/ [Accessed 18 Juni 2022].

15. Libby, G., Donnelly, L.A., Donnan, P.T., Alessi, D.R., Morris, A.D. and Evans, J.M.M. (2012). Lower risk of cancer in patients on metformin in comparison with those on sulfonylurea derivatives: results from a large population-based follow-up study. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/22100960/ [Accessed 18 Juni 2022].

16. Soranna, D., Scotti, L., Zambon, A., Bosetti, C., Grassi, G., Catapano, A., La Vecchia, C. and Mancia, G. (2012). Metformin and Sulfonylureas in Relation to Cancer Risk in Type II Diabetes Patients: A Meta-Analysis Using Primary Data of Published Studies. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/23419783/ [Accessed 18 Juni 2022].

17. Tang, G., Wang, J., Wang, L., Zhang, S., Liu, H., Li, H., Liu, X. and Xu, Y. (2022). Does metformin reduce the risk of cancer in obesity and diabetes? A systematic review and meta-analysis. *PubMed*, [online] [Accessed 18 Juni 2022].

18. Tang, G.H., Satkunam, M., Pond, G.R., Steinberg, G.R., Blandino, G., Schünemann, H.J. and Muti, P. (2014). Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/24898303/ [Accessed 18 Juni 2022].

19. Landman, G.W.D., Kleefstra, N., van Hateren, K.J.J., Groenier, K.H., Gans, R.O.B. and Bilo, H.J.G. (2010). Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/19918015/ [Accessed 18 Juni 2022].

20. Bowker, S.L., Majumdar, S.R., Veugelers, P. and Johnson, J.A. (2006). Increased Cancer-Related Mortality for Patients With Type 2 Diabetes Who Use Sulfonylureas or Insulin. *Diabetes Care*, [online] 29(2), pp.254–258. Available at: https://diabetesjournals.org/care/article/29/2/254/26229/Increased-Cancer-Related-Mortality-for-Patients [Accessed 18 Juni 2022].

21. Johnson, J.A. and Bowker, S.L. (2009). Metformin, Cancer, Alphabet Soup, and the Role of Epidemiology in Etiologic Research. *PMC*, [online] Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2732134/ [Accessed 18 Juni 2022].

22. Bodmer, M., Meier, C., Krähenbühl, S., Jick, S.S. and Meier, C.R. (2009). New users of metformin are at low risk of incident cancer: a cohort study among

people with type 2 diabetes. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/19564453/ [Accessed 18 Juni 2022].

23. Gandini, S., Puntoni, M., Heckman-Stoddard, B.M., Dunn, B.K., Ford, L., DeCensi, A. and Szabo, E. (2011). Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *NCBI*, [online] Available at: https://www.ncbi.nlm.nih.gov/books/NBK80660/ [Accessed 18 Juni 2022].

24. Zhang, P., Li, H., Tan, X., Chen, L. and Wang, S. (2012). Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/22448244/ [Accessed 18 Juni 2022].

25. Lin, H.C., Hsu, Y.T., Kachingwe, B.H., Hsu, C.Y., Wang, J.J. and Cheng, K.C. (2022). Association of metformin use and cancer incidence: a systematic review and meta-analysis of observational studies. *PMC*, [online] [Accessed 18 Juni 2022].

26. Li, D., Yeung, S.C.J., Hassan, M.M., Konopleva, M. and Abbruzzese, J.L. (2009). Antidiabetic therapies affect risk of pancreatic cancer. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/19375425/ [Accessed 18 Juni 2022].

27. Spillane, S., Bennett, K., Sharp, L. and Barron, T.I. (2015). Effect of Metformin on Cancer Risk and Treatment Outcome of Prostate Cancer: A Meta-Analysis of Epidemiological Observational Studies. *PLOS ONE*, [online] Available at: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0116327&type=printable [Accessed 18 Juni 2022].

28. Bodmer, M., Becker, C., Meier, C., Jick, S.S. and Meier, C.R. (2010). Long-term metformin use is associated with decreased risk of breast cancer. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/20299480/ [Accessed 18 Juni 2022].

29. Donadon, V., Balbi, M., Mas, M.D., Casarin, P. and Zanette, G. (2010). Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/20331505/ [Accessed 18 Juni 2022].

30. Zhang, Z.J., Zheng, Z.J. and Shi, R. (2012). Metformin and Hepatocellular Carcinoma. *Harvard DASH*, [online] Available at: https://dash.harvard.edu/bitstreams/7312037d-e0ab-6bd4-e053-0100007fdf3b/download [Accessed 18 Juni 2022].

31. Morden, N.E., Liu, S.K., Smith, J., Mackenzie, T.A., Skinner, J. and Korc, M. (2011). Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/20980415/ [Accessed 18 Juni 2022].

32. Lee, J.H., Kim, T.I., Jeon, S.M., Hong, S.P., Cheon, J.H. and Kim, W.H. (2011). Reduced Risk of Colorectal Cancer With Metformin Therapy in Patients With Type 2 Diabetes: A Meta-analysis. *Diabetes Care*, [online] 34(10), pp.2323–2328. Available at: https://diabetesjournals.org/care/article-pdf/34/10/2323/606474/2323.pdf [Accessed 18 Juni 2022].

33. Yin, M., Zhou, J., Gorak, E.J. and Quddus, F. (2013). Metformin in cancer prevention and therapy. *PMC*, [online] Available

at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4200668/ [Accessed 18 Juni 2022].

34. Tseng, C.H. (2014). Long-term metformin use reduces gastric cancer risk in type 2 diabetics without insulin treatment: a population-based cohort study. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/24612291/ [Accessed 18 Juni 2022].

35. Zhang, Z.J., Yuan, J., Bi, Y., Wang, C. and Liu, Y. (2014). Reduced Risk of Lung Cancer With Metformin Therapy in Diabetic Patients: A Systematic Review and Meta-Analysis. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/24920786/ [Accessed 18 Juni 2022].

36. Xiao, Y., Zhang, S., Hou, G., Zhang, X., Hao, X. and Zhang, J. (2018). Association of Metformin with Breast Cancer Incidence and Mortality in Patients with Type II Diabetes: A GRADE-Assessed Systematic Review and Meta-analysis. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/29618465/ [Accessed 18 Juni 2022].

37. Pubrica Academy (2021). Assessing Study Quality in Meta-Analysis using Newcastle-Ottawa Scale. *Pubrica Academy*, [online] Available at: https://pubrica.com/academy/meta-analysis/assessing-study-quality-in-meta-analysis-using-newcastle-ottawa-scale/ [Accessed 18 Juni 2022].

38. Wikipedia (2022). Newcastle–Ottawa scale. *Wikipedia*, [online] [Accessed 18 Juni 2022].

39. Pope, B. and Bruce, C. (n.d.). The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta- Analysis. *Evidence-based*

Public Health, [online] Available at: https://www.evidencebasedpublichealth.de/download/Newcastle_Ottowa_Scale_Pope_Bruce.pdf [Accessed 18 Juni 2022].

40. Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. and Tugwell, P. (n.d.). Newcastle-Ottawa Quality Assessment Scale. *The Ottawa Hospital*, [online] Available at: https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Accessed 18 Juni 2022].

41. Oh, T.K. and Song, I.A. (2020). Metformin and risk of cancer among patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *PubMed*, [online] Available at: https://pubmed.ncbi.nlm.nih.gov/32605879/ [Accessed 18 Juni 2022].

42. Landman, G.W.D., Kleefstra, N., van Hateren, K.J.J., Groenier, K.H., Gans, R.O.B. and Bilo, H.J.G. (2010). Metformin Associated With Lower Cancer Mortality in Type 2 Diabetes. *Semantic Scholar*, [online] Available at: https://www.semanticscholar.org/paper/Metformin-Associated-With-Lower-Cancer-Mortality-in-Landman-Kleefstra/690a2dadd176dbdfff54843de659558519c2fe42 [Accessed 18 Juni 2022].

43. Lee, H., Lee, J., Kang, S.Y., Do, H.G., Park, H.E., Lee, E.S. and Kim, H.C. (2018). Correlation between metformin intake and prostate cancer. *Journal of Cancer Prevention & Current Research*, [online] 9(2). Available at: https://www.e-jcpp.org/journal/view.php?number=75 [Accessed 18 Juni 2022].

44. Johnson, J.A. and Bowker, S.L. (2009). Metformin, Cancer, Alphabet Soup, and the Role of Epidemiology in Etiologic Research. *Diabetes Care*, [online] 32(9), pp.1748–1755. Available at: https://diabetesjournals.org/care/article/32/9/1748/28852/Metformin-Cancer-Alphabet-Soup-and-the-Role-of [Accessed 18 Juni 2022].