Metformin for Cancer Care: Review of Studies to Discover Who Benefits

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Study context and question

Cancer patients are increasingly hearing that metformin may improve treatment outcomes, and are requesting a prescription. However, metformin use is accompanied by some serious side effects.

- Toxicity during chemotherapy
- Gastrointestinal symptoms, anemia, and hormone imbalances

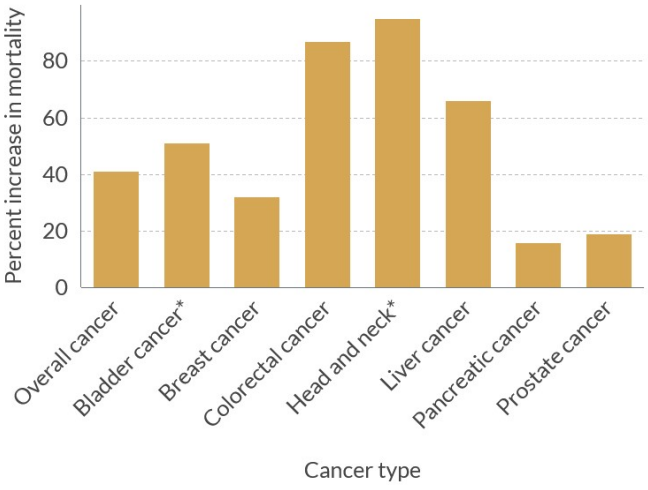
Use without evidence of benefit is not recommended. We investigated this question: **When is metformin use indicated among people with cancer?**

We reviewed and analyzed the evidence of efficacy in cancer care so that oncology professionals can better inform, guide and advise their patients in off-label use of metformin.

Clinical significance

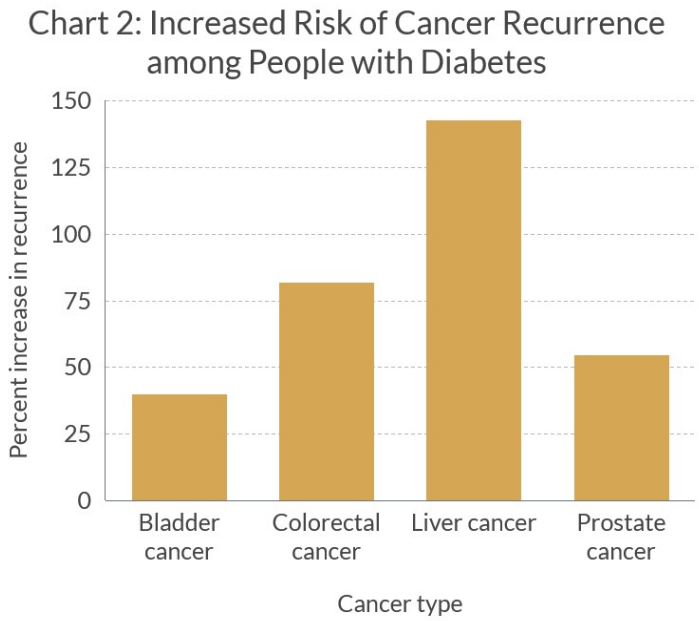
People with diabetes are at substantially higher risks of mortality and recurrence.

Chart 1: Increase in Relative Mortality among People with Cancer Who Also Have Diabetes



Note: Studies reported different mortality time points, from one year to more than eight years. Some studies reported mortality among more specific populations, such as people at a specific cancer stage or with a specific subtype of cancer. When more than one study reported differing numbers on mortality, we used the more conservative numbers.

*Cancer-specific survival; all others are overall survival



Assembling the evidence

- We selected 193 clinical studies from Pubmed through March 2022 on metformin's use in cancer care.
- Studies related to cancer treatment outcomes, body terrain factors linked to cancer growth and spread such as insulin resistance or inflammation, symptoms/side effects, and risk of cancer or recurrence.

Interpreting the evidence

Studies have reported conflicting outcomes regarding impacts of metformin use on survival or risks of recurrence or incidence of cancer.

We categorized studies by treatment outcome, cancer type, population diabetes/metabolism status, treatment doses, timing, duration, and other characteristics.

We found that treatment outcome and risk of recurrence were closely linked to the study samples' diabetes/metabolism status: better outcomes and lower risk were found consistently among people with diabetes or prediabetes treated with metformin, but much less consistently among people with normal glycemic/metabolic status treated with metformin.

For a deeper analysis of the potential interaction of glycemic status and metformin use on cancer response, survival, and recurrence, we further analyzed studies investigating these effects. We found that study designs vary substantially on characteristics of treatment and comparison groups.

Comparing outcomes from people using metformin for diabetes treatment to cancer outcomes from people without diabetes is an apples-to-oranges comparison due to the higher baseline risks of mortality and recurrence that accompany diabetes. We reviewed only studies with similar intervention and control groups to better interpret the effects of metformin use.

Included studies

For this analysis, we included studies with these designs:

1. RCTs, controlled trials, observational studies, and subgroup analyses of these, in which both the intervention and comparison groups are clearly similar regarding status of diabetes or other metabolic disorders
2. Meta-analyses in which a clear majority of the individual studies (roughly weighted by study population size) fit criterion 1. For other meta-analyses, we reviewed the individual studies that conformed to criterion 1 above.

We categorized 89 studies:

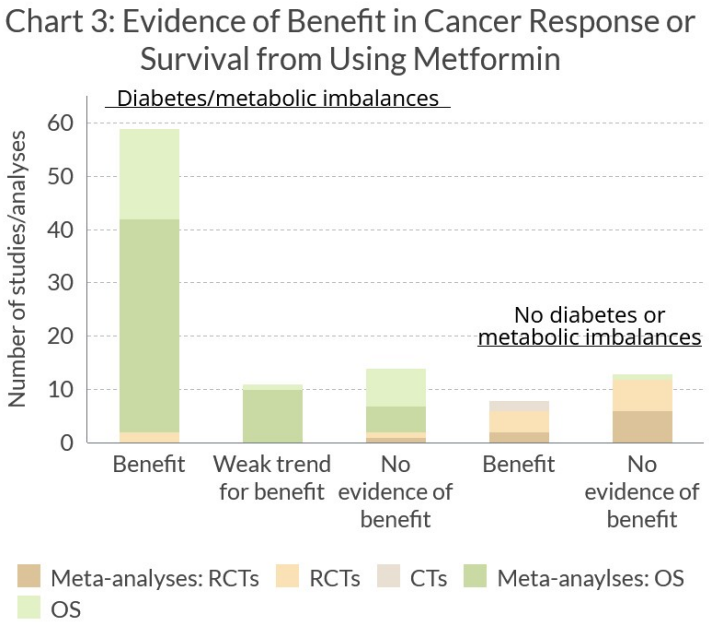
- 5 meta-analyses of RCTs
- 12 individual RCTs not included in meta-analyses
- 2 controlled trials
- 45 meta-analyses of observational studies
- 25 individual observational studies not included in meta-analyses.

Findings

Anticancer response or improved survival

For most cancer types and for cancer as a whole:

- For people with diabetes or metabolic imbalances, the bulk of evidence shows an advantage in survival or anticancer response for using metformin.
- For people with advanced cancer and diabetes, **no** evidence shows a survival benefit from using metformin.
- For people without diabetes or metabolic imbalances, the evidence is less clear but leans toward **no advantage in survival or anticancer response** from using metformin.



RCT = randomized controlled trial, OS = observational study, CT = controlled trial

Benefit ($p \leq 0.05$), Weak trend ($p <$ about 0.1 but > 0.05), No evidence of an effect ($p >$ about 0.1)

Table 1. Evidence of benefit in cancer response or survival from using metformin by cancer type					
	People with diabetes/metabolic imbalances			**People without diabetes/metabolic imbalances**	
Cancer type	**Response or survival benefit**	**Weak trend toward benefit**	**No evidence of benefit**	**Response or survival benefit**	**No evidence of benefit**
Cancer as a whole	3 meta-analyses of OS				
Advanced cancer			1 meta-analysis of RCTs		
Bladder	2 meta-analyses of OS				
Brain (glioma, glioblastoma)	3 OS				
Breast (both ER+ and ER-)	2 RCTs, 2 meta-analyses of OS, 1 OS	1 meta-analysis of OS, 1 OS	1 RCT, 1 OS	1 meta-analysis of RCTs, 4 RCTs	4 meta-analyses of RCTs, 2 RCTs
Breast ER- only		1 OS	1 OS	1 RCT	
Breast ER+ only	1 OS				
Cervical			1 OS		
Colorectal	6 meta-analyses of OS, 1 OS	3 meta-analyses of OS			
Endometrial	8 meta-analyses of OS			2 controlled trials	1 RCT, 1 OS
Esophageal					1 RCT
Gastric		1 meta-analysis of OS			
Head and neck	1 meta-analysis of OS and 4 OS				

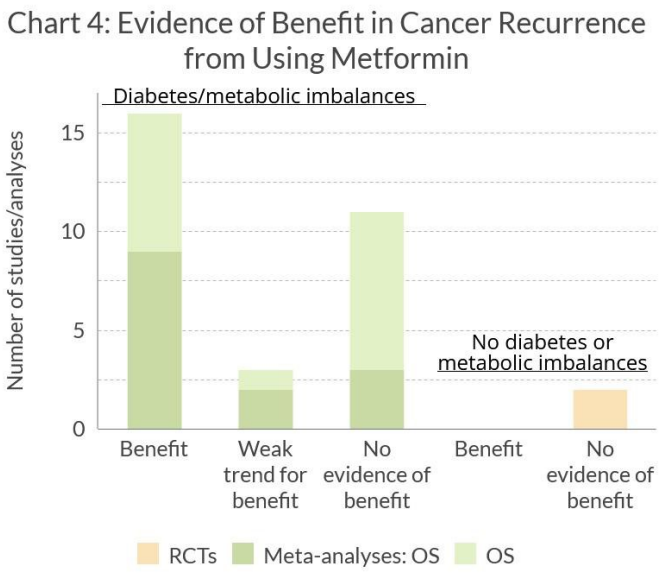
Kidney	2 meta-analyses of OS		1 meta-analysis of OS and 1 OS		
Leukemia	1 RCT				
Liver	1 meta-analysis of OS	1 meta-analysis of OS			
Lung	5 meta-analyses of OS and 2 OS	1 meta-analysis of OS	1 OS	1 meta-analysis of RCTs	1 meta-analysis of RCTs
Lymphoma	1 OS		1 OS		
Melanoma					1 RCT
Ovarian	3 meta-analyses of OS and 3 OS	1 meta-analysis of OS	1 OS		1 RCT
Pancreatic	4 meta-analyses of OS and 1 OS				1 meta-analysis of RCTs
Prostate	3 meta-analyses of OS	2 meta-analyses of OS	3 meta-analyses of OS		
Urothelial			1 meta-analysis of OS		

Lower risk of recurrence

Among people with diabetes or metabolic imbalances, any advantage in lower risk of recurrence shows considerable variation from one type of cancer to another. The clearest evidence of benefit to date is for these cancer types:

Bladder	Colorectal	Head and neck	Ovarian
Cervical	Endometrial	Liver	Prostate

For people without diabetes or metabolic imbalances, only limited evidence is available but shows **no advantage from using metformin on recurrence**.



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Benefit ($p \leq 0.05$), Weak trend ($p <$ about 0.1 but > 0.05), No evidence of an effect ($p >$ about 0.1)

Table 2. Evidence of benefit in cancer recurrence from using metformin by cancer type

	People with diabetes/metabolic imbalances			People without diabetes/metabolic imbalances	
Cancer type	**Recurrence benefit**	**Weak trend toward benefit**	**No evidence of benefit**	**Recurrence benefit**	**No evidence of benefit**
Bladder	1 meta-analysis of OS	1 meta-analysis of OS			
Breast (both ER+ and ER-)	1 OS		1 meta-analysis of OS, 2 OS		1 RCT
Breast ER-only			2 OS		
Breast ER+ only	1 OS				
Cervical	1 OS				
Colorectal	1 meta-analysis	1 meta-analysis			

	of OS, 1 OS	of OS			
Endometrial	1 meta-analysis of OS				
Head and neck	3 OS				
Kidney			1 OS		
Liver	1 meta-analysis of OS		1 OS		
Lung			2 OS		
Ovarian		1 OS			1 RCT
Prostate	5 meta-analyses of OS		1 meta-analysis of OS		
Urothelial			1 meta-analysis of OS		

Evidence of harm

Some evidence shows worse outcomes with some cancer types among people **without diabetes/metabolic imbalances** using metformin:

- Higher markers of proliferation among nondiabetic people with breast cancer and low insulin resistance
- Higher mortality among nondiabetic people with liver cancer treated with metformin
- Higher rates of adverse events including treatment failure, disease progression, and death during platinum-based chemotherapy concurrent with chest radiotherapy among nondiabetic people with locally advanced non-small cell lung cancer treated with metformin

Conclusions

- Metformin use may reduce or even eliminate the increased risks of poor survival and recurrence among people with both cancer and diabetes.
- Research to date has not found a clear indication of improved survival or lower risk of recurrence among people with cancer with normal glycemic/metabolism status, and some evidence shows worse response or outcomes with some cancer types.

Implications for practice

Oncology professionals can take these steps:

- Learn about benefits/risks of metformin as an off-label anticancer therapy and indications for use. See cancerchoices.org/therapy/metformin/

- Provide trustworthy information about benefits and risks regarding use; find a patient education sheet at cancerchoices.org/therapy/metformin/for-health-professionals/
- Develop in-house policies about prescribing and monitoring anticancer metformin use.
- Refer patients to trustworthy outside licensed clinicians, if appropriate.

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