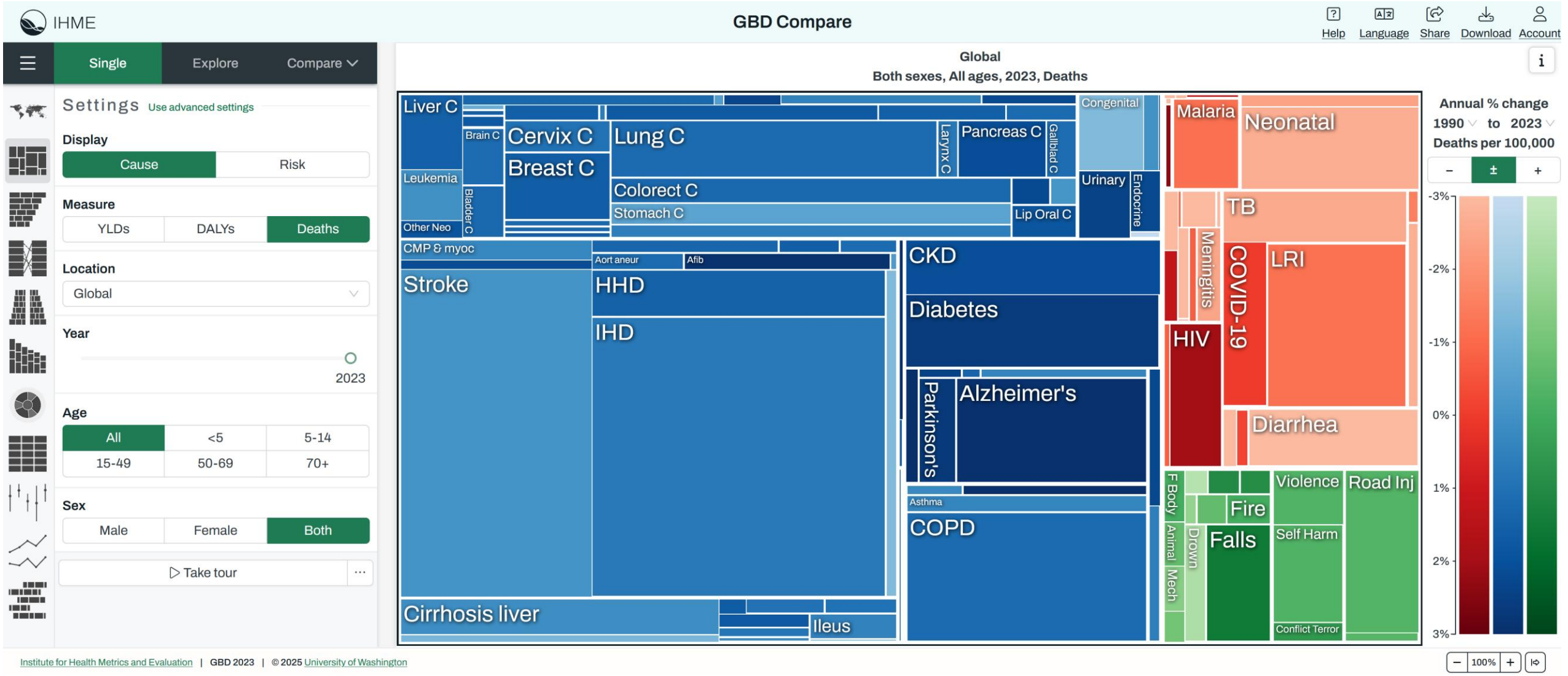
Cancer prevention AND Metformin

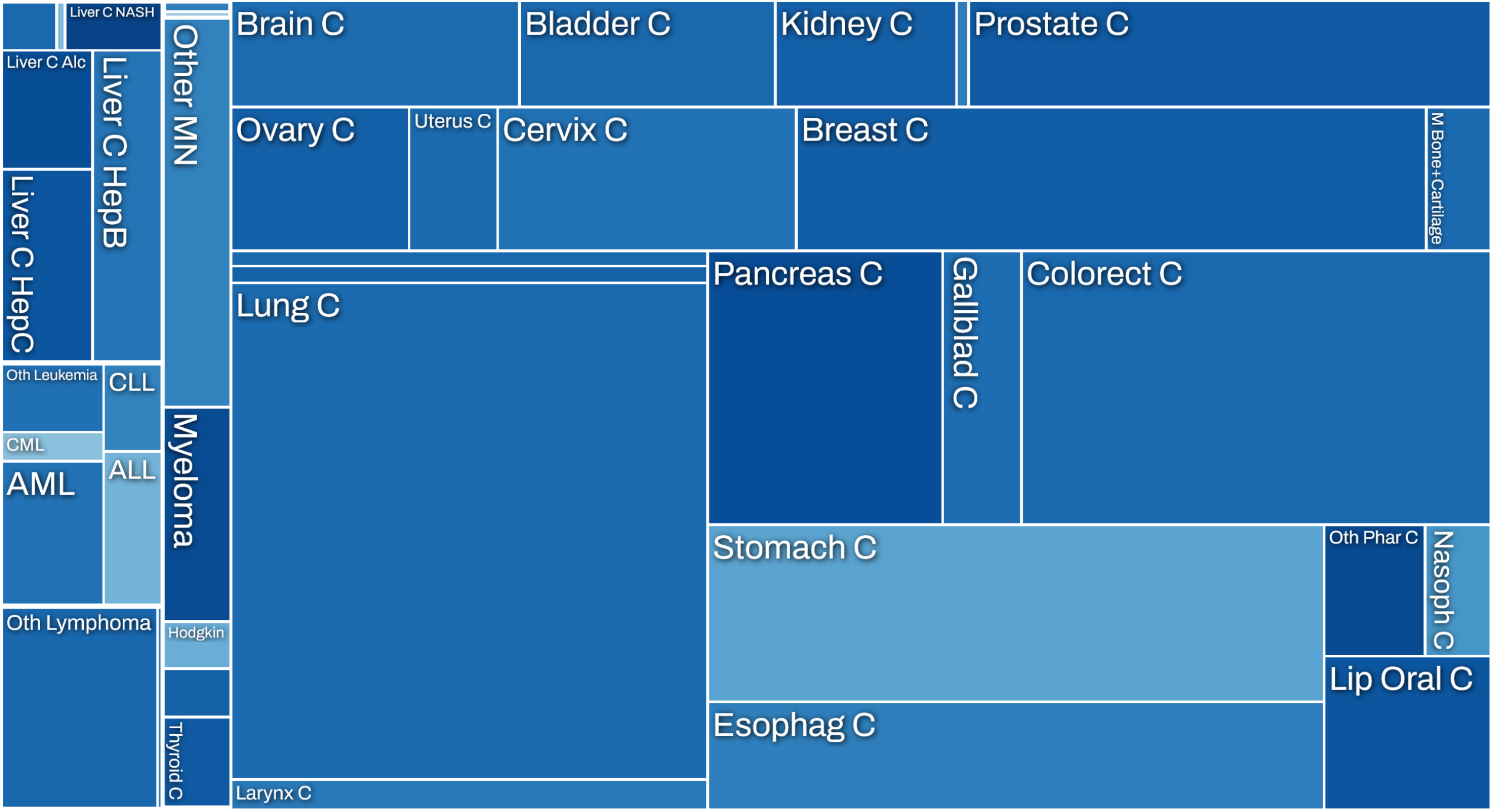
Majid Sorouri, Gastroenterologist

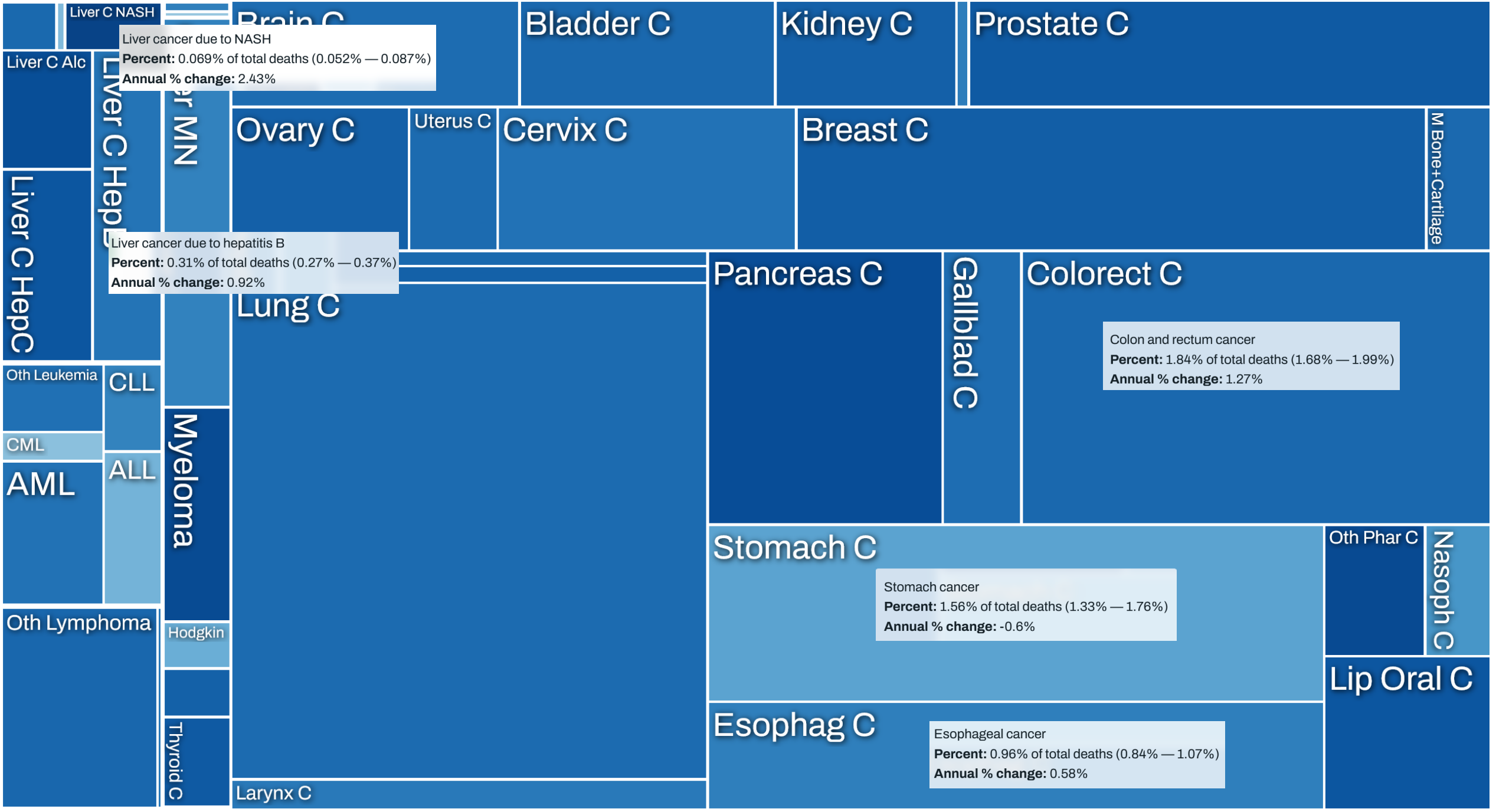
Shariati hospital, DDRI, TUMS.

Oct, 30, 2025

https://vizhub.healthdata.org/gbd-compare/

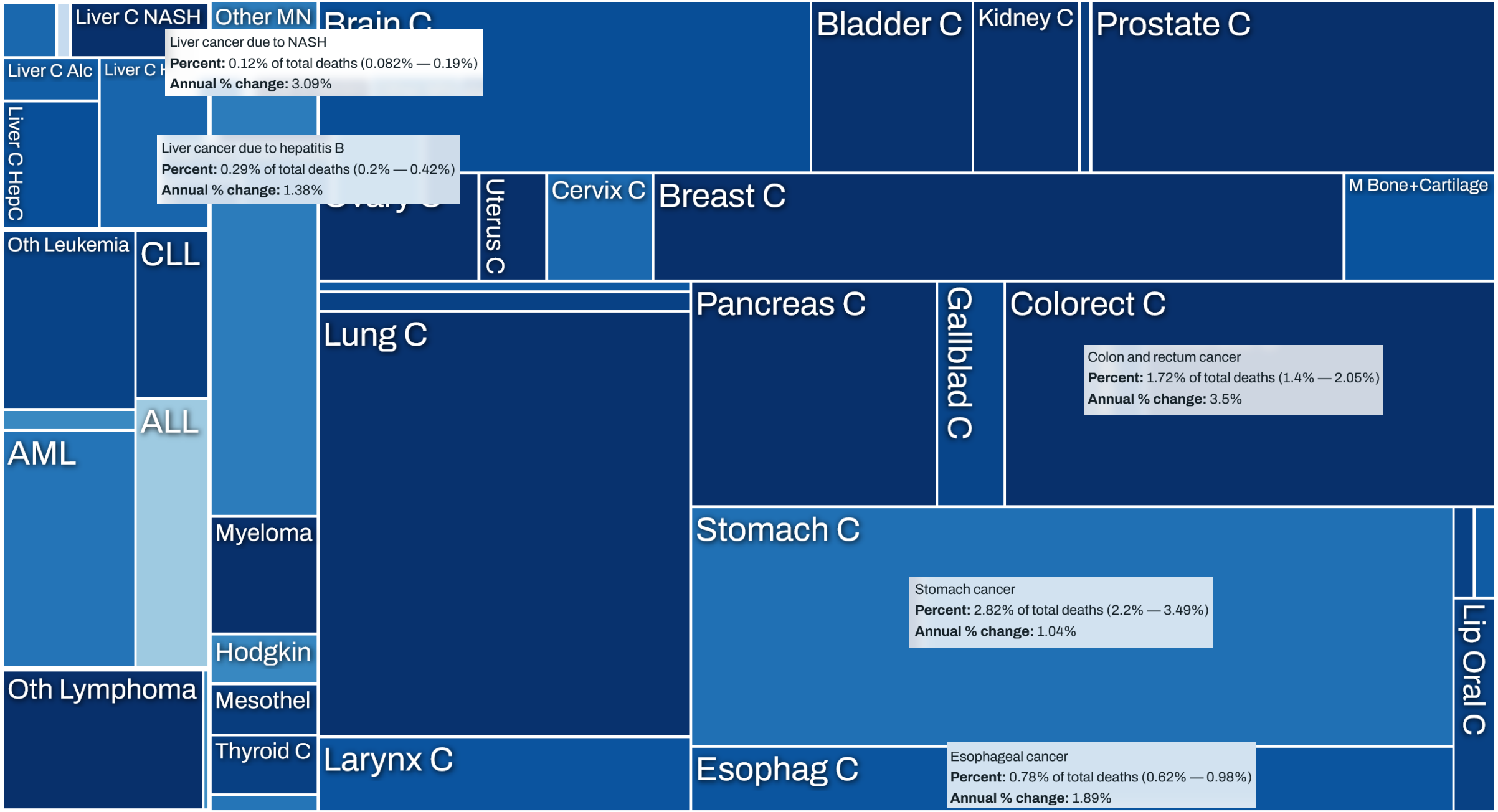



Liver C NASH
Liver C Alc
Liver C HepB
Liver C HepC
Other MN
Brain C
Bladder C
Kidney C
Prostate C
Ovary C
Uterus C
Cervix C
Breast C
M Bone+Cartilage
Lung C
Pancreas C
Gallblad C
Colorect C
Oth Leukemia
CLL
CML
AML
ALL
Myeloma
Hodgkin
Thyroid C
Oth Lymphoma
Larynx C
Stomach C
Oth Phar C
Nasoph C
Lip Oral C
Esophag C


Liver C NASH
Liver cancer due to NASH
Percent: 0.069% of total deaths (0.052% — 0.087%)
Annual % change: 2.43%
Brain C
Bladder C
Kidney C
Prostate C
Liver C Alc
Liver C Hep
er MN
Ovary C
Uterus C
Cervix C
Breast C
M Bone+Cartilage
Liver C HepC
Liver cancer due to hepatitis B
Percent: 0.31% of total deaths (0.27% — 0.37%)
Annual % change: 0.92%
Lung C
Pancreas C
Gallblad C
Colorect C
Colon and rectum cancer
Percent: 1.84% of total deaths (1.68% — 1.99%)
Annual % change: 1.27%
Oth Leukemia
CLL
CML
AML
ALL
Myeloma
Stomach C
Stomach cancer
Percent: 1.56% of total deaths (1.33% — 1.76%)
Annual % change: -0.6%
Oth Phar C
Nasoph C
Oth Lymphoma
Hodgkin
Lip Oral C
Esophag C
Esophageal cancer
Percent: 0.96% of total deaths (0.84% — 1.07%)
Annual % change: 0.58%
Thyroid C
Larynx C

Iran (Islamic Republic of)

Both sexes, All ages, 2023, Deaths



Global

Colon and rectum cancer
Percent: 1.84% of total deaths (1.68% — 1.99%)
Annual % change: 1.27%

Stomach cancer
Percent: 1.56% of total deaths (1.33% — 1.76%)
Annual % change: -0.6%

Esophageal cancer
Percent: 0.96% of total deaths (0.84% — 1.07%)
Annual % change: 0.58%

Liver cancer due to NASH
Percent: 0.069% of total deaths (0.052% — 0.087%)
Annual % change: 2.43%

Liver cancer due to hepatitis B
Percent: 0.31% of total deaths (0.27% — 0.37%)
Annual % change: 0.92%

Iran

Colon and rectum cancer
Percent: 1.72% of total deaths (1.4% — 2.05%)
Annual % change: 3.5%

Stomach cancer
Percent: 2.82% of total deaths (2.2% — 3.49%)
Annual % change: 1.04%

Esophageal cancer
Percent: 0.78% of total deaths (0.62% — 0.98%)
Annual % change: 1.89%

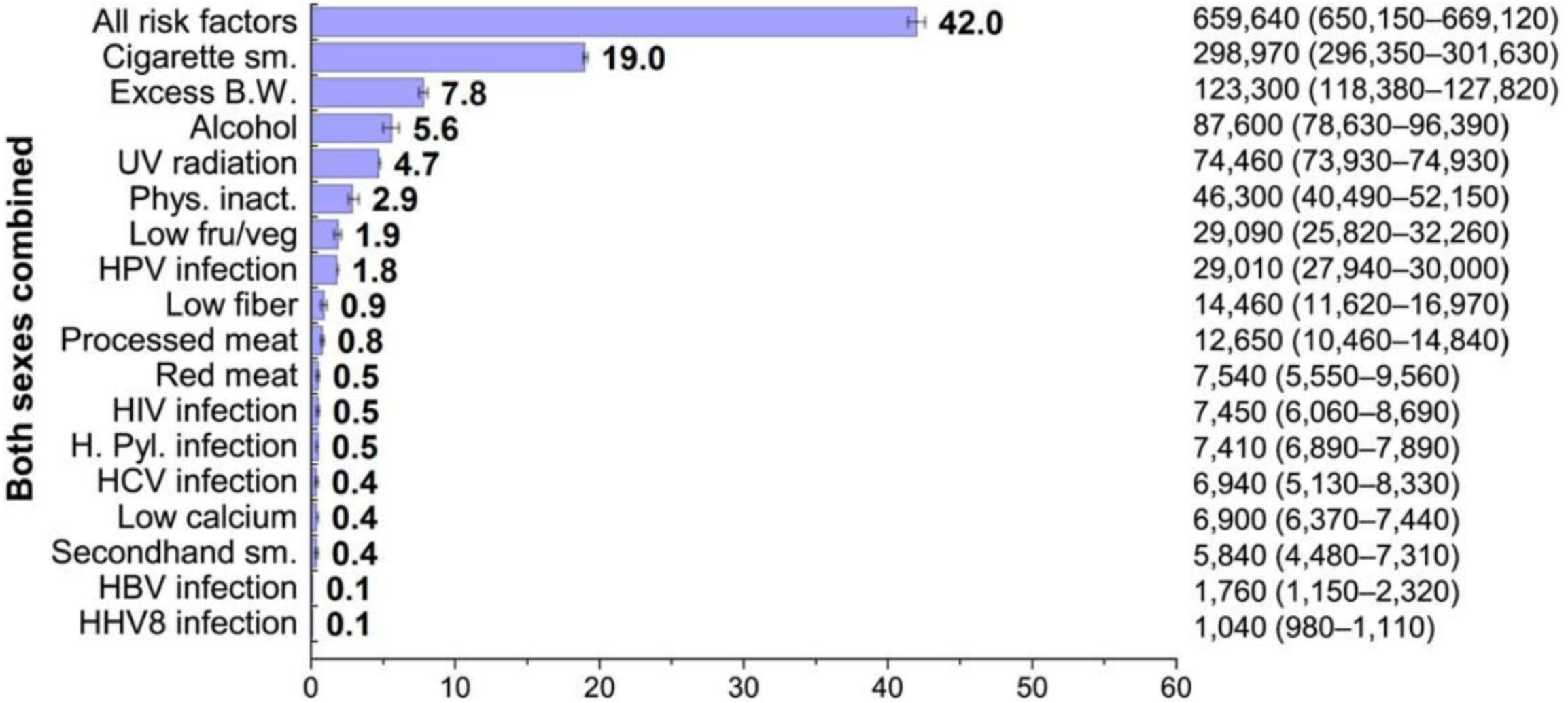
Liver cancer due to NASH
Percent: 0.12% of total deaths (0.082% — 0.19%)
Annual % change: 3.09%

Liver cancer due to hepatitis B
Percent: 0.29% of total deaths (0.2% — 0.42%)
Annual % change: 1.38%

Population attributable fraction (PAF)

the fraction of all cases of a particular disease or other adverse

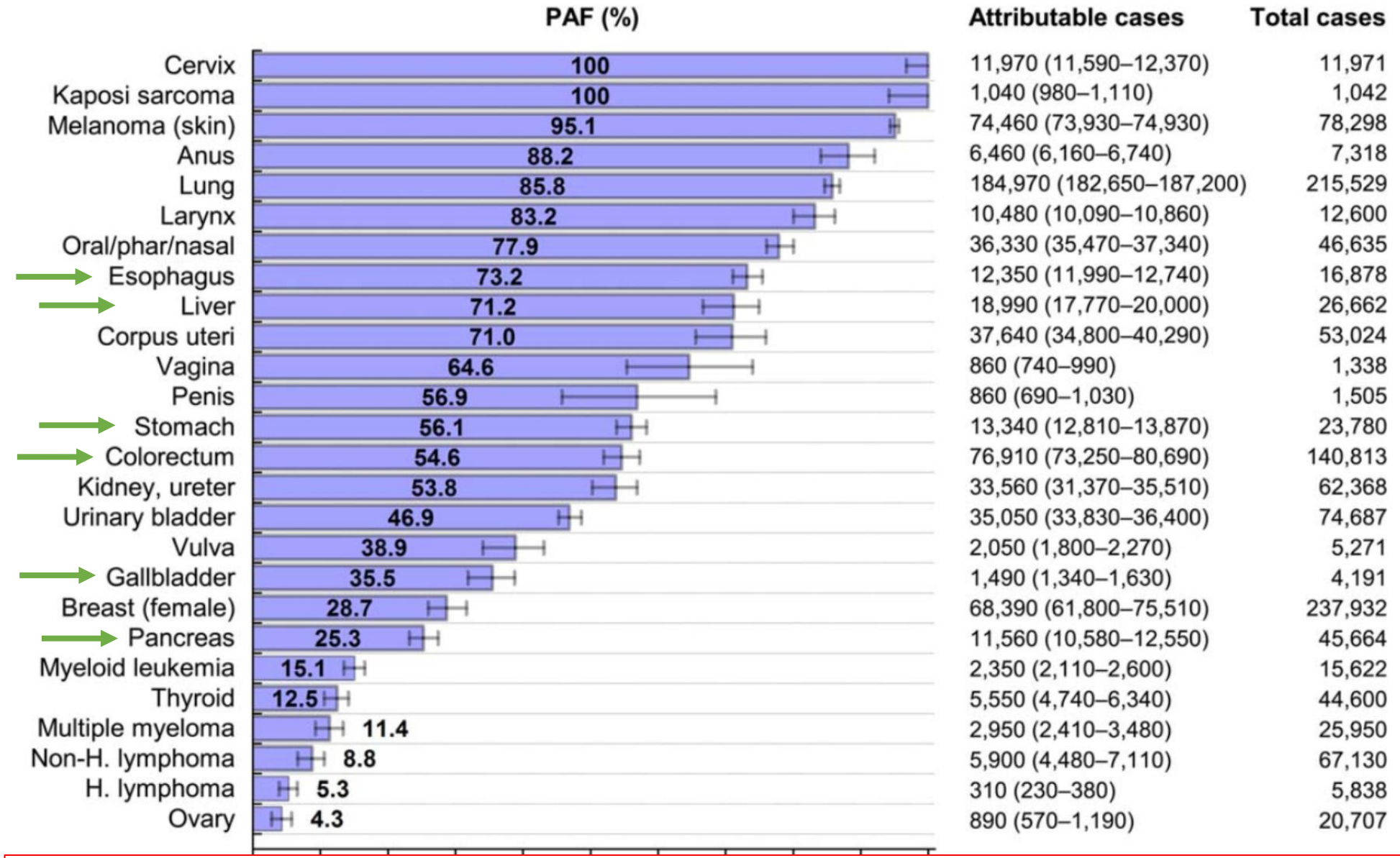
condition in a population that is attributable to a specific exposure



Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors in Adults Aged 30 Years and Older in the United States in 2014, by Sex.

The total number of all incident cancer cases (excluding nonmelanoma skin cancer cases) in adults aged 30 years and older was 782,210 among men, 788,765 among women, and 1570,975 for both sexes combined.
The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer cases and deaths are rounded to the nearest 10.

Islami F, etal. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018 Jan;68(1):31-54.



Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors and Number of Total Cases in Adults Aged 30 Years and Older in the United States in 2014, by Cancer Type.

The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer cases are rounded to the nearest 10.

Islami F, etal. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018 Jan;68(1):31-54.

Chemoprevention

- ASA
- Metformin
- Warfarin
- Statins
- Oral Contraceptives
- Selective estrogen receptor modulators, Aromatase inhibitors (Breast cancer)
- 5-alpha reductase inhibitors (Prostate cancer)
- …

Metformin

Metformin has been shown to affect cancer cell proliferation in in vitro and in vivo studies.

- act on protein synthesis via the AMP activated protein kinase (AMPK) and mTOR signaling pathways
- Inhibits the mitochondrial respiratory chain complex on tumor cells, increasing the activation of the AMPK pathway
- lowering of glycemia and reduction in insulin resistance, resulting in lower insulin and insulin-like growth factor 1 (IGF-1) levels

1. Breast cancer
2. Colon ca
3. Prostate ca
4. Endometrial ca
5. Ovarian ca
6. Lung ca
7. Brain ca

Yu OHY, Suissa S. Metformin and Cancer: Solutions to a Real-World Evidence Failure. Diabetes Care. 2023 May 1;46(5):904-912.

RESEARCH POINTERS

Metformin and reduced risk of cancer in diabetic patients

Josie M M Evans, Louise A Donnelly, Alistair M Emslie-Smith, Dario R Alessi, Andrew D Morris

Observational case-control analysis

A clinical database of over 11,000 patients with type 2 diabetes from Scotland.

923 cancer / 1,846 matched control subjects

a significant 23% reduction in the incidence of any cancer associated with metformin use

Evans JM, etal.. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005 Jun 4;330(7503):1304-5.

Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis

- Systematic review of 5 observational studies
- 108,161 patients with type 2 DM
- Mean follow-up: 2.4 – 5.6 years
- metformin use associated with decreased risk of :

	Relative Risk	RR CI95%	Number of studies
✓ Colon cancer	O.63	0.47-0.84	4
✓ Colon neoplasia	0.63	0.5-0.79	5

Zhang ZJ, etal.. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. Diabetes Care. **2011** Oct;34(10):2323-8.

Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis

- SR: Randomized trial (2), Cohort studies(8), Case control studies (5)
- 840,787 patients with DM (primarily type 2 diabetes).
- 13,871 patients had colorectal cancer.
- Meta-analysis included only observational studies.

- Metformin associated with decreased risk of Colorectal cancer:
  - Adjusted Odds Ratio = 0.89 (CI95%= 0.81 – 0.99)
  - Analysis of 9 studies, results limited by significant heterogeneity



- No significant association with risk of colorectal cancer with:
  - Thiazolidindiones
  - Sulfonylurea
  - Insulin



Singh S, etal.. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. **2013** Dec;22(12):2258-68.

Colon neoplasia in patients with type 2 diabetes on metformin: A meta-analysis

- SR: Randomized trial (1), Cohort studies(13), Case control studies (3)
- 709,980 patients with type 2 diabetes.
- All results limited by significant heterogeneity.
- Compared to no use, metformin use associated with decreased risk of:

	Relative Risk	RR CI95%	Number of studies
✓ Colon cancer	O.79	0.69-0.91	14
✓ Colon polyp	0.58	0.42-0.8	3
✓ Colon neoplasia	0.75	0.65-0.87	17

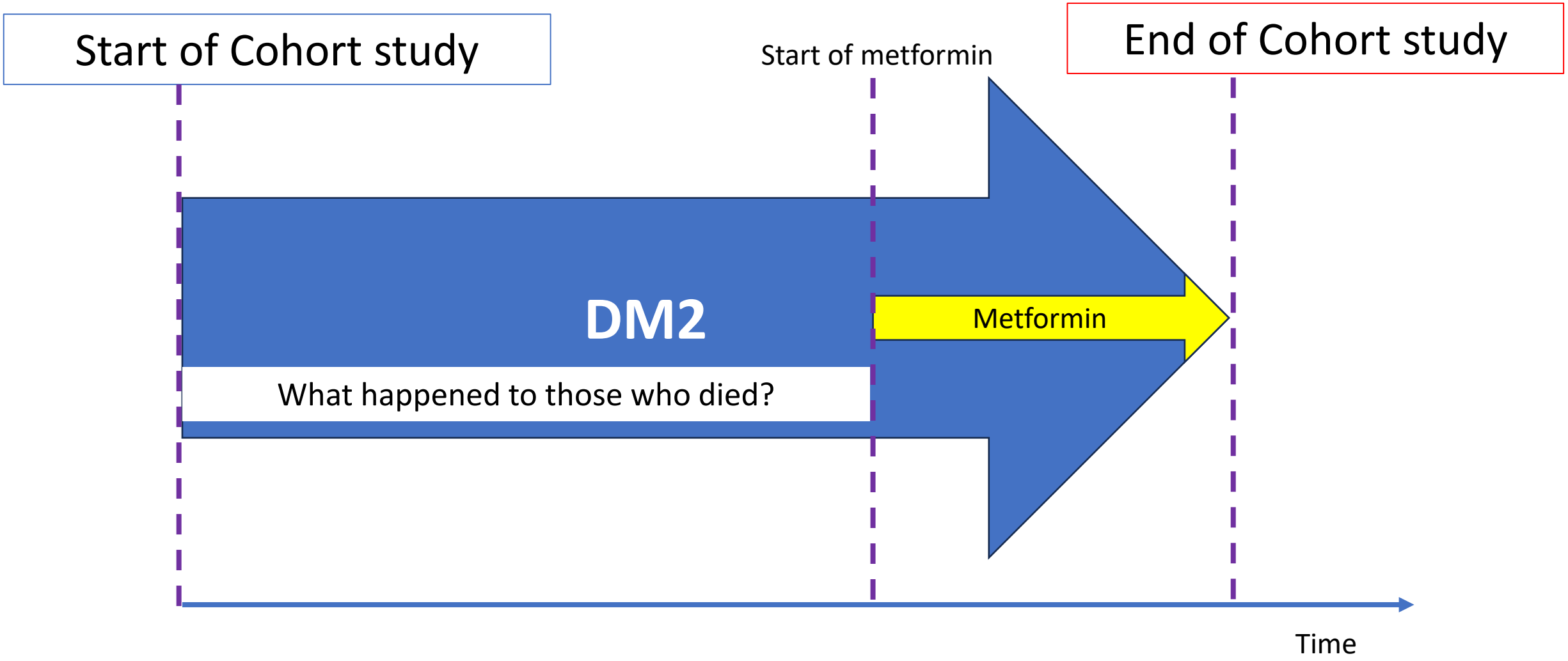
Rokkas T, etal. Colon neoplasia in patients with type 2 diabetes on metformin: A meta-analysis. Eur J Intern Med. **2016** Sep;33:60-6.

Immortal Time Bias in Cohort Studies: A Concept Simply Explained

Chittaranjan Andrade[1]

immortal time bias occurs when formal observation of patients starts before patients experience the exposure, and when, by design, patients who experience the outcome of interest before they experience the exposure of interest are ineligible to be included in the exposure arm of the study.

Andrade C. Immortal Time Bias in Cohort Studies: A Concept Simply Explained.
Indian J Psychol Med. 2025 May 19;47(4):408-409.


Start of Cohort study
Start of metformin
End of Cohort study
DM2
Metformin
What happened to those who died?
Time

Int J Colorectal Dis. 2022 Aug;37(8):1827-1834. doi: 10.1007/s00384-022-04212-9. Epub 2022 Jul 14.

Metformin use is not associated with colorectal cancer incidence in type-2 diabetes patients: evidence from methods that avoid immortal time bias

Hyun-Soo Zhang [1 2], Yeunsoo Yang [3 4], Sunmi Lee [5], Sohee Park [6], Chung Mo Nam [1 2 7], Sun Ha Jee [4]

- A total of 41,533 Korean subjects with newly diagnosed type-2 diabetes in 2005-2015 were selected from a prospectively maintained cohort (median follow-up of 6.3 years).
- Neither metformin ever-use nor average metformin prescription days/year was associated with incident CRC hazard in time-dependent Cox, landmark, and nested case-control analyses
- time-fixed Cox regression showed a falsely exaggerated protective effect of metformin on CRC incidence.

Zhang HS, etal.. Metformin use is not associated with colorectal cancer incidence in type-2 diabetes patients: evidence from methods that avoid immortal time bias. Int J Colorectal Dis. 2022 Aug;37(8):1827-1834.

Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis

- Systematic review of 5 observational studies
  - Prospective Cohort studies(2), Retrospective Cohort studies(1), Case control studies (2)
  - 105,495 patients with type 2 diabetes.

- All results limited by significant heterogeneity.
- Metformin use associated with decreased risk of:

	Odds Ratio	RR - CI95%	Number of studies
✓ Primary liver cancer	O.38	0.24-0.59	5
✓ HCC	0.3	0.17-0.52	4

Zhang ZJ, etal.. Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab. **2012** Jul;97(7):2347-53.

Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis

- Systematic review of 10 observational studies
- 334,307 patients with type 2 DM

- Metformin use associated with decreased risk of :
  - HCC : Odds Ratio=0.5 (CI95%= 0.34 – 0.73)
  - Analysis of 8 studies, results limited by significant heterogeneity

- No association with decreased risk of HCC with:
  - Thiazolidindiones (n=4; OR 0.54, 95% CI 0.28-1.02). Not significant
  - Sulfonylurea (n=8 studies; OR 1.62, 95% CI 1.16-2.24) Increased risk
  - Insulin (n=7; OR 2.61, 95% CI 1.46-4.65) Increased risk

Singh S, etal.. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. Am J Gastroenterol. **2013** Jun;108(6):881-91; quiz 892.

OXFORD

JNCI: Journal of the National Cancer Institute, 2024, **116(4),** 518–529

https://doi.org/10.1093/jnci/djae021
Advance Access Publication Date: January 30, 2024
Review

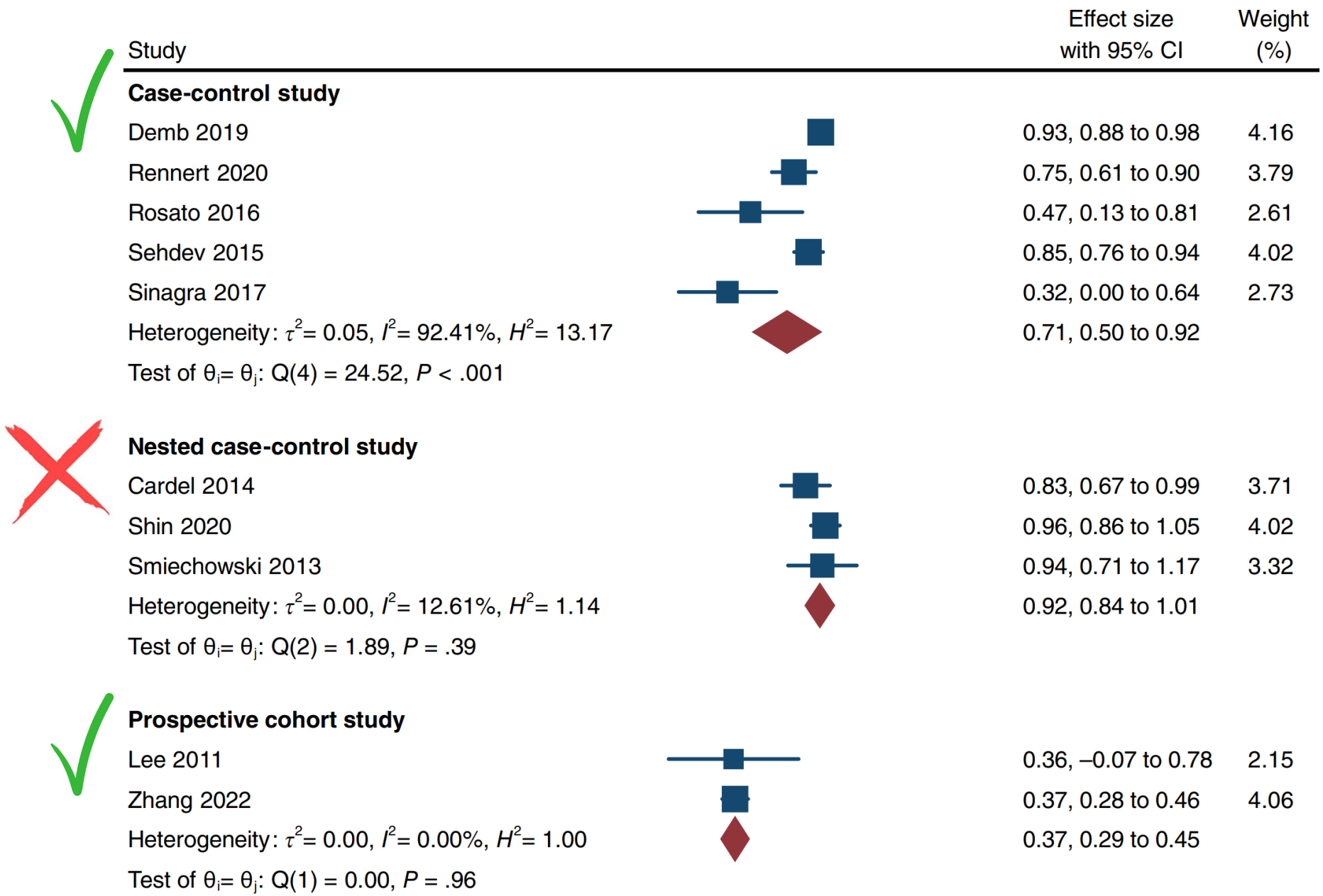
Association of metformin use and cancer incidence: a systematic review and meta-analysis

Lauren O'Connor, PhD, MPH,[1] Maeve Bailey-Whyte, PhD, MPH,[2] Manami Bhattacharya, PhD, MS,[3] Gisela Butera, MLIS, MA,[4] Kaitlyn N. Lewis Hardell, PhD, MPH,[1,5] Andrew B. Seidenberg, PhD, MPH,[6,7] Philip E. Castle, PhD, MPH,[8] Holli A. Loomans-Kropp, PhD, MPH[9,10,11,*]

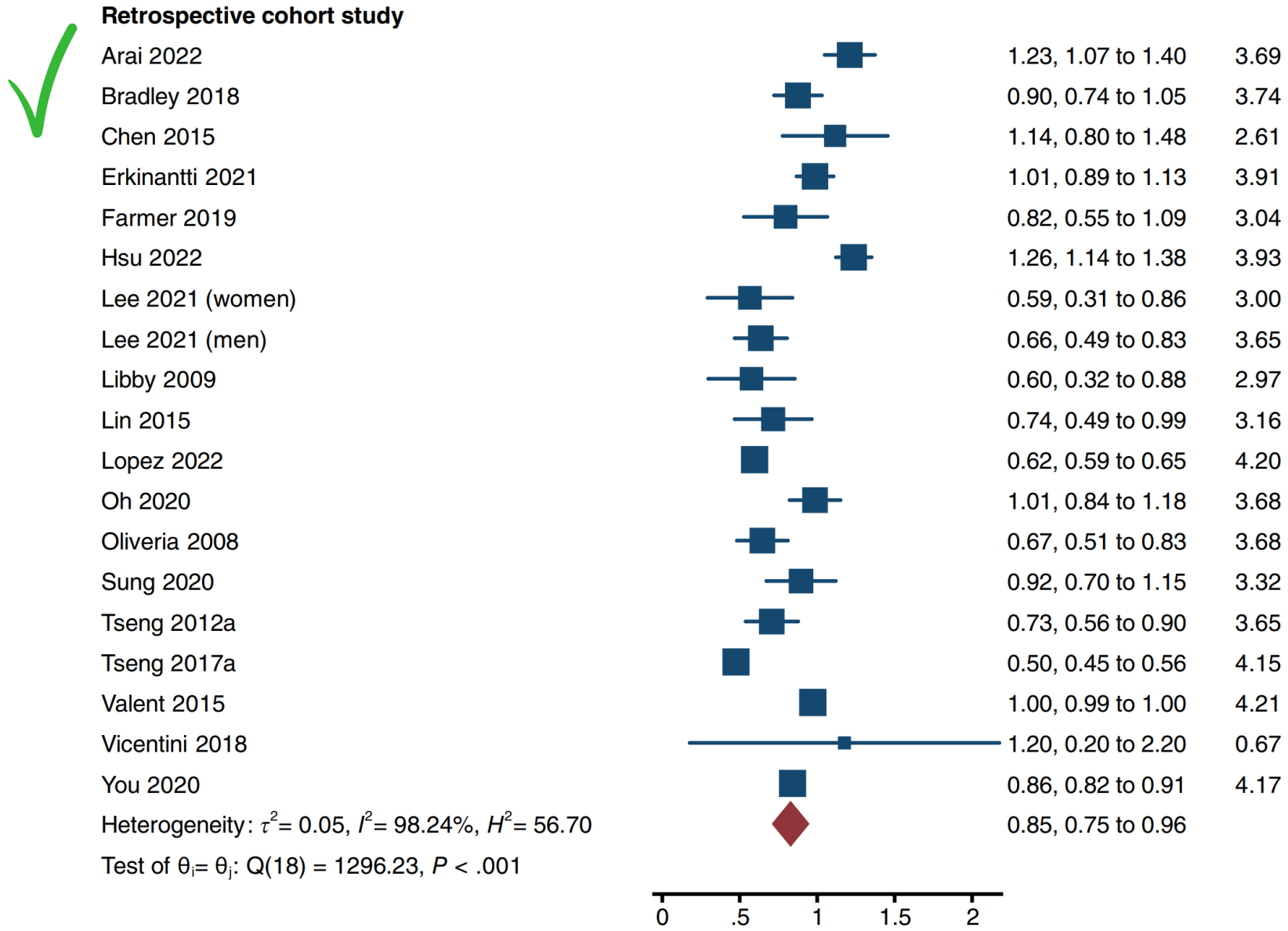
Metformin use was associated with a statistically significant reduction in ***overall*** cancer incidence.

✓
- prospective studies: RR = 0.65, (CI 95% = 0.37 to 0.93); I^2 = 98.0%
- case-control studies: RR = 0.55, (CI 95% = 0.30 to 0.80); I^2 = 98.5%

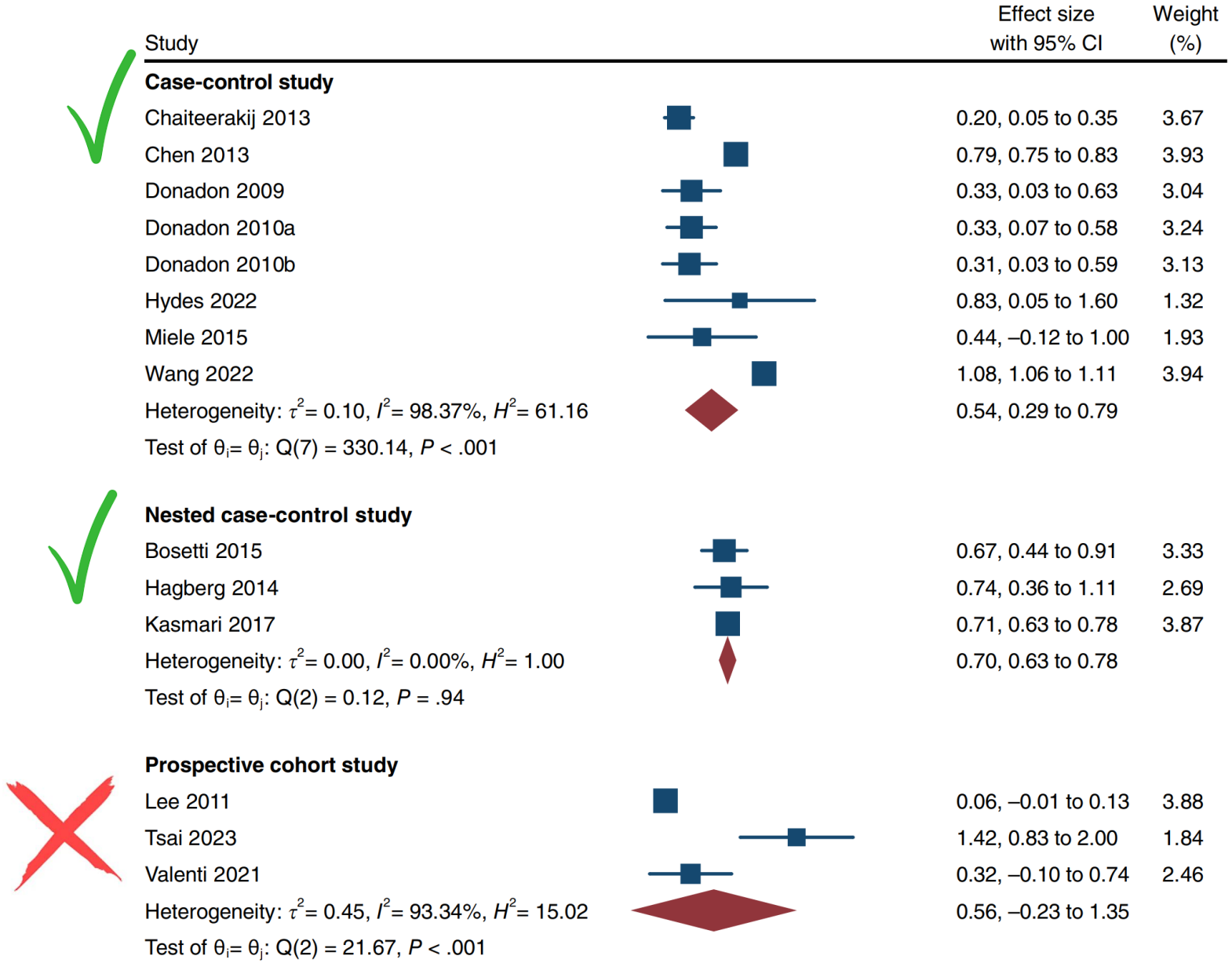
✗
- cross-sectional studies: RR= 0.96, (CI 95% = 0.67 to 1.24); I^2 = 0.0%
- retrospective cohort studies: RR= 0.86, (CI 95% = 0.70 to 1.03); I^2=99.9%



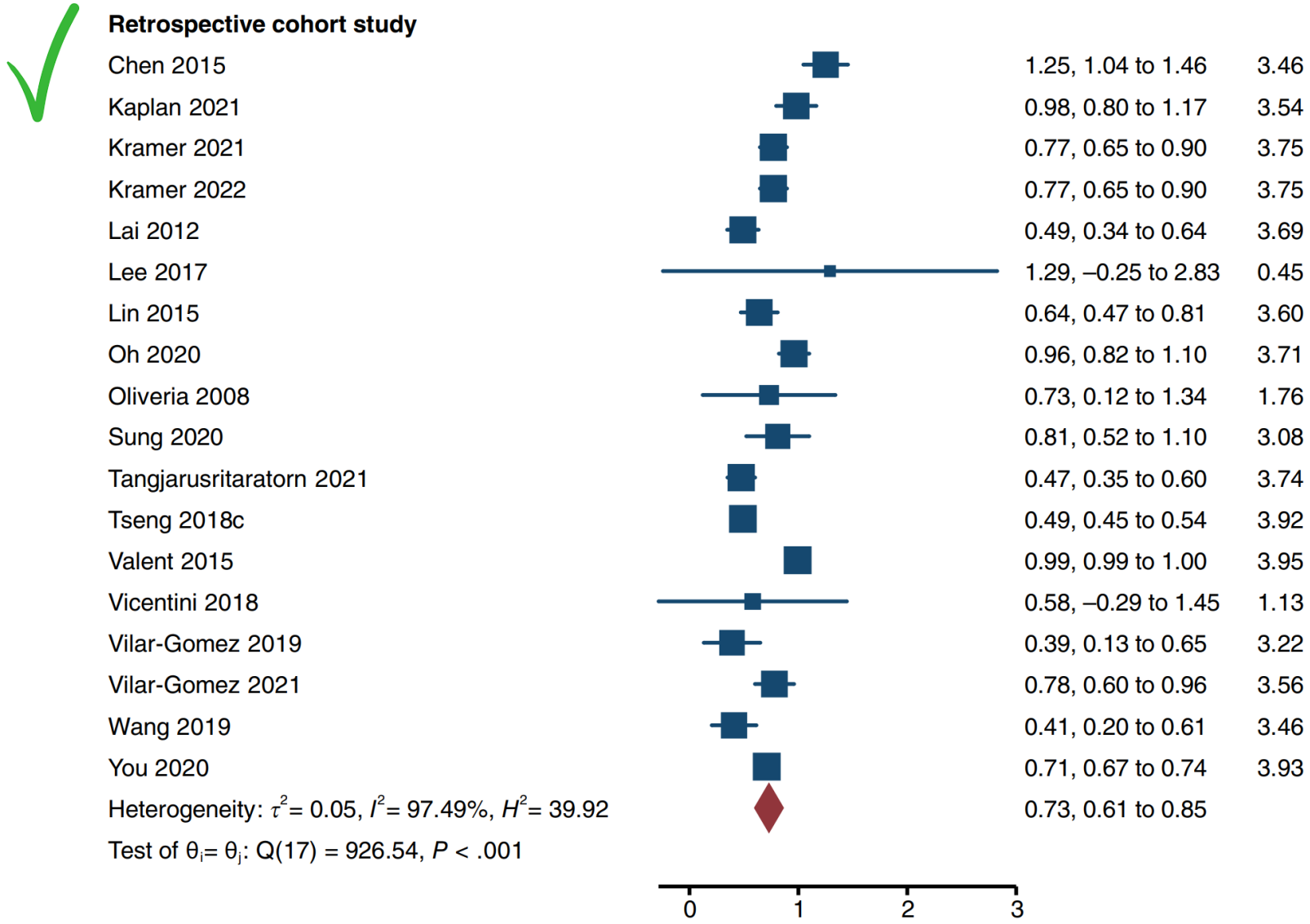
Estimated summary relative risk for **colorectal cancer** with metformin use in a random-effects model.



Estimated summary relative risk for **colorectal cancer** with metformin use in a random-effects model.



Estimated summary relative risk for **liver cancer** with metformin use in a random-effects model.



Estimated summary relative risk for **liver cancer** with metformin use in a random-effects model.

Table 1. Estimated summary relative risks and corresponding 95% confidence intervals for the association between metformin use and other cancers in a random-effects model[a]

Cancer type	Estimates included, No.	Summary relative risk (95% confidence interval)	Heterogeneity I^2, H^2	Bias test: Egger, Begg
Bile duct or biliary tract	4	0.82 (0.54 to 1.11)	93.3%, 14.91	<0.001, 0.73
Bladder	5	0.70 (0.56 to 0.83)	61.3%, 2.59	0.01, 0.22
Bone	3	0.90 (0.74 to 1.06)	30.2%, 1.43	0.57, 1.00
Cervical	3	0.68 (0.49 to 0.87)	50.3%, 2.01	0.61, 1.00
Endometrial	6	1.12 (0.89 to 1.35)	72.9%, 3.69	<0.001, 0.71
Esophageal	12	0.68 (0.50 to 0.86)	88.5%, 8.71	<0.001, 0.13
Gastric	15	0.76 (0.63 to 0.89)	94.8%, 28.73	<0.001, 0.14
Head and neck or oral	8	0.58 (0.45 to 0.72)	65.8%, 2.92	0.35, 0.90
Kidney	3	0.66 (0.12 to 1.19)	92.6%, 13.55	<0.001, 1.00
Lung	19	0.88 (0.76 to 0.99)	90.9%, 11.00	0.01, 0.15
Ovarian	2	0.53 (0.21 to 0.85)	73.3%, 3.75	NC
Pancreatic	15	1.13 (0.86 to 1.40)	95.6%, 22.92	0.04, 0.06
Skin	5	0.86 (0.63 to 1.09)	78.4%, 4.62	0.14, 0.81
Thyroid	6	0.74 (0.51 to 0.97)	81.9%, 5.53	0.02, 1.00

[a] Estimates of publication bias are indicated in this table by the Begg test and in Supplementary Figure 1 (available online) (funnel plot). NC = not calculated.

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Cancer type	Estimates included, No.	Summary relative risk (95% confidence interval)	Heterogeneity I^2, H^2	Bias test: Egger, Begg
Bile duct or biliary tract ✕	4	0.82 (0.54 to 1.11)	93.3%, 14.91	<0.001, 0.73
Bladder	5	0.70 (0.56 to 0.83)	61.3%, 2.59	0.01, 0.22
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[a] Estimates of publication bias are indicated in this table by the Begg test and in Supplementary Figure 1 (available online) (funnel plot). NC = not calculated.

Table 2. Estimated summary relative risk and corresponding 95% confidence interval for the association between metformin use and cancer risk by organ system in a random-effects model[a]

Organ system	Estimates included, No.	Summary relative risk (95% confidence interval)	Heterogeneity I^2, H^2	Bias test: Egger, Begg
Gastrointestinal	110	0.79 (0.73 to 0.85)	99.9%, 2624.94	0.04, <0.001
Gynecologic	13	1.03 (0.75 to 1.31)	96.4% 27.75	0.23, 0.20
Hematologic	8	0.87 (0.75 to 0.99)	72.0%, 3.57	0.59, 0.71
Urologic	41	0.88 (0.78 to 0.99)	98.3%, 58.48	<0.001

[a] Measures of study heterogeneity and bias are included.

- The results of this meta-analysis suggest that metformin use, compared with no metformin use, is associated with a decreased risk of overall cancer as well as several cancer subtypes, largely for populations that have *type 2 diabetes*.

- these results should be interpreted with *caution* due to:
  - ✓ high heterogeneity in study design
  - ✓ risk for publication bias.

- Future cancer prevention trials for *nondiabetic* populations would further elucidate the preventative potential of metformin.

THE LANCET
Oncology

ARTICLES · Volume 17, Issue 4, P475-483, April 2016 Download Full Issue



Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial

Takuma Higurashi, MD [a] · Kunihiro Hosono, MD [a] · Hirokazu Takahashi, MD [a] · Yasuhiko Komiya, MD [a] · Shotaro Umezawa, MD [a] · Eiji Sakai, MD [a] · et al. Show more

Higurashi T, etal.. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial.
Lancet Oncol. 2016 Apr;17(4):475-483.

✓A multicentre, double-blind, placebo-controlled, randomised phase 3 trial.

✓Non-diabetic adult + single/multiple colorectal adenomas or polyps resected by endoscopy

✓five hospitals in Japan.

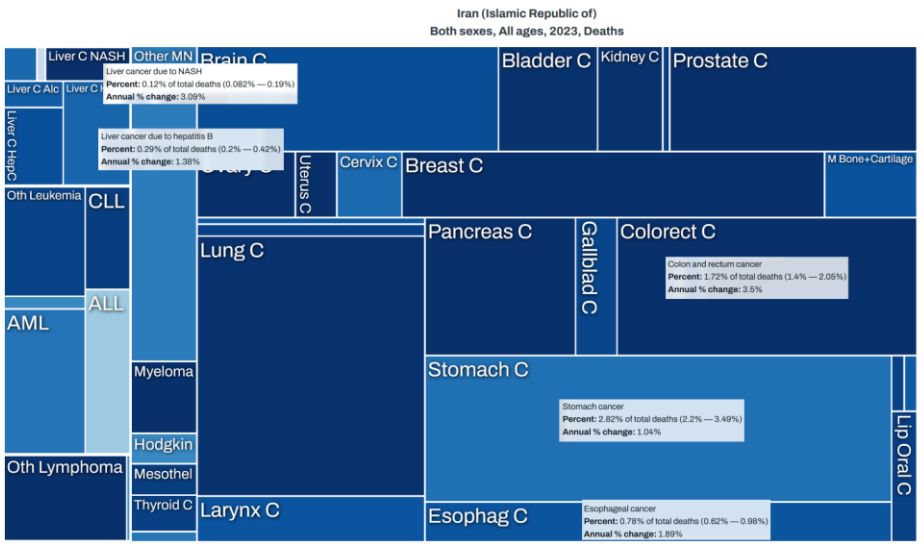
✓randomly assigned (1:1) : oral metformin (250 mg daily) / placebo tablets

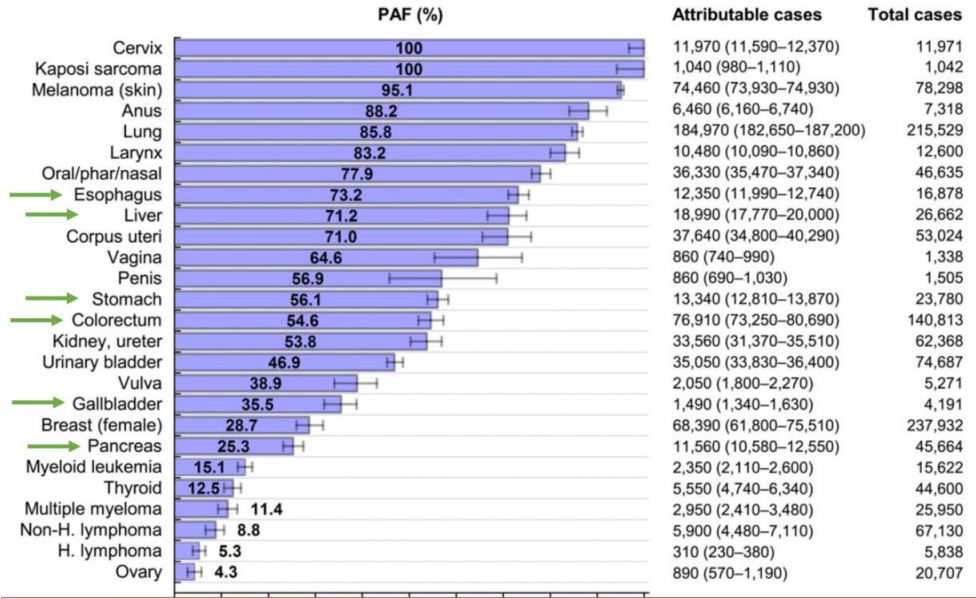
✓After 1 year of administration of metformin or placebo, colonoscopies were done

✓the intention-to-treat principle.

NNT total polyps= 5.4
NNT adenomas = 4.8

	Metformin (250 mg daily)	Placebo	P value
N	79	72	
1-year follow-up colonoscopy	71 (90%)	62 (86%)	
total polyps (hyperplastic polyps + adenomas)	27 (**38**%)	35 (**56.5**%)	0.034
adenomas	22 (30.6%)	32(51.6%)	0.016
adverse events	15 (11%) all = grade 1 no serious adverse events during the 1-year trial		





Estimated Proportion and Number of Incident Cancer Cases Attributable to Evaluated Risk Factors and Number of Total Cases in Adults Aged 30 Years and Older in the United States in 2014, by Cancer Type.

The bars in the figure and numbers in parentheses represent 95% confidence intervals. Numbers of attributable cancer cases are rounded to the nearest 10.

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Metformin use was associated with a statistically significant reduction in ***overall*** cancer incidence.

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- retrospective cohort studies: RR= 0.86, (CI 95% = 0.70 to 1.03); I^2=99.9%

✓A multicentre, double-blind, placebo-controlled, randomised phase 3 trial.

✓Non-diabetic adult + single/multiple colorectal adenomas or polyps resected by endoscopy

✓five hospitals in Japan.

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