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Meeting

September 7 & 8, 2023

9<sup>th</sup> edition

# Profile of cancer-related excess mortality in NAFLD

JF Dufour, Switzerland





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# Conflict of interest disclosure

- Advisory committees: Alentis, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Enyo, Esai, Genfit, Gilead Sciences, Intercept, Inventiva, Ipsen, Madrigal, MSD, Novartis, Novo-Nordisk, Roche.
- Speaking and teaching: Bristol-Myers Squibb, Intercept, Ipsen, Gilead Sciences, Roche





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# Agenda

- Cancer mortality in NAFLD patients
- Cancer, which Cancers ?
- Clinical implications



# Percent distribution of cause of death in NAFLD

## Angulo al. Gastroenterology 2015

- Retrospective analysis of 619 patients diagnosed with NAFLD from 1975 through 2005 in the United States, Europe, and Thailand

Outcome	Number
Death or OLT	<i>n</i> = 193
Cardiovascular disease	74 (38.3%)
Non-liver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8%)
Others	35 (18.1%)



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# Causes of death in NAFLD patients

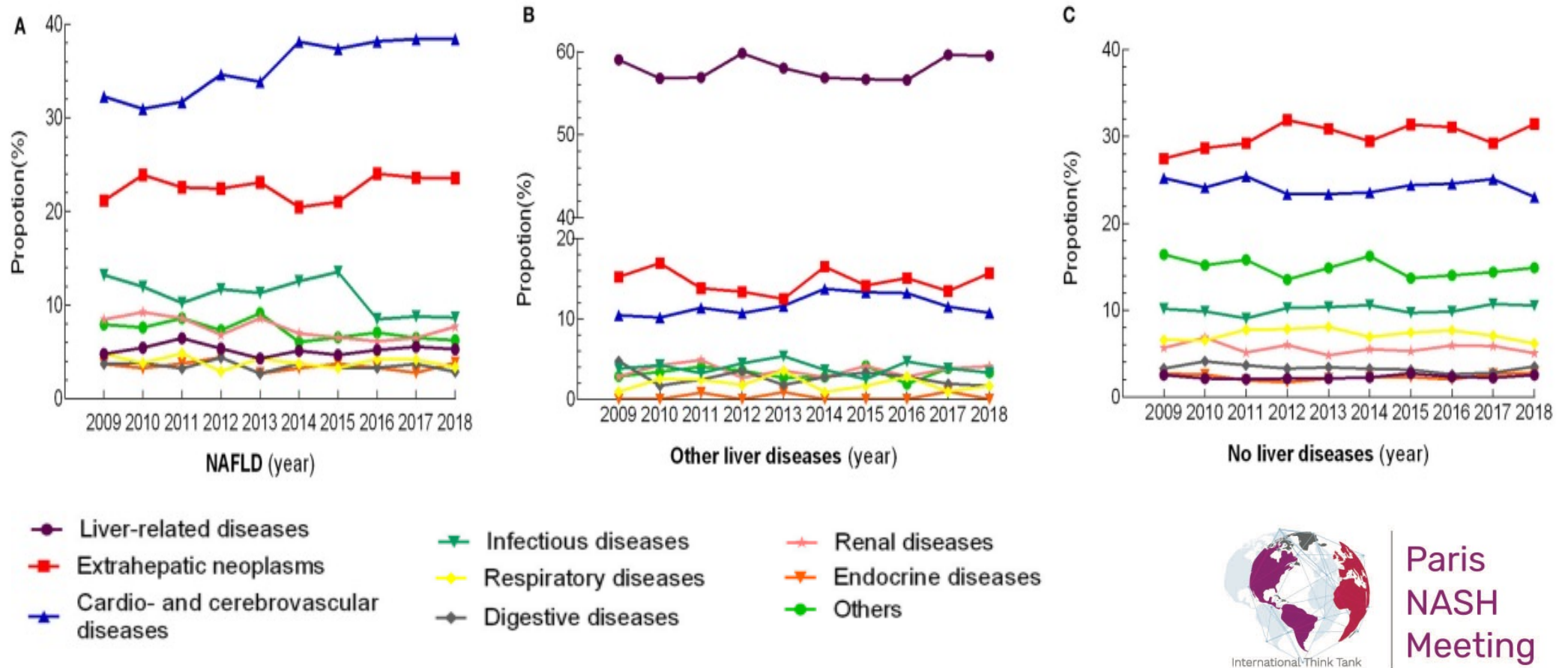
- Lin et al. Frontiers in Medicine 2021
- Chinese multicenter retrospective investigation with a 10-year study period (2009–2018) analyzed 10,071 deaths during hospitalization (NAFLD: 2,015; other liver diseases: 1,140; without liver diseases: 6,916).
- NAFLD : ultrasound criteria for fatty liver, no excessive alcohol intake (>20 g/day in men and >10 g/day in women) and negative markers of hepatitis B and C
- The underlying causes of death were classified by 10th Revision of the International Classification of Diseases (ICD-10) codes.



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# Causes of death in NAFLD patients



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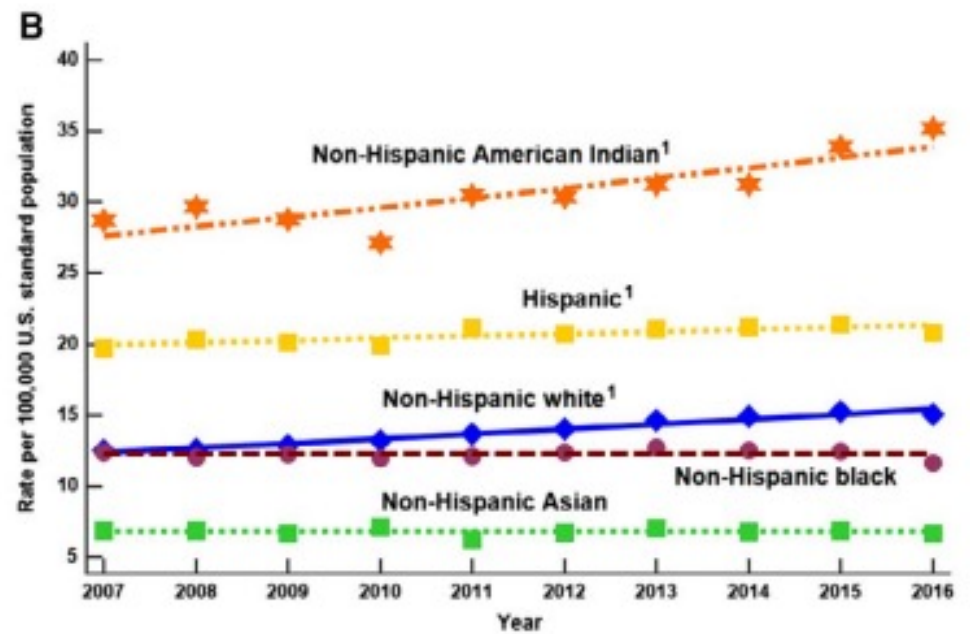
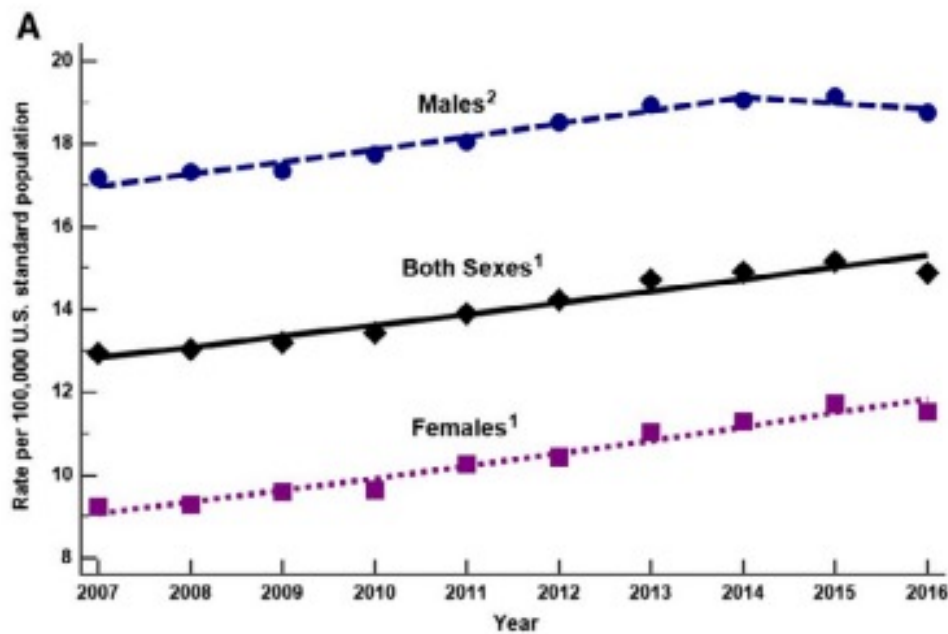
# Trend of mortality related to NAFLD

- Paik et al. Hepatology Communications 2019
- Data from the US National Vital Statistics System (2007-2016)
- NAFLD cases et cause-specific deaths identified by ICD codes
- Trends evaluated by average annual percentage change (AAPC) in age-standardized death rate (ASDR) per 100,000 person.



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# Trend of mortality related to NAFLD

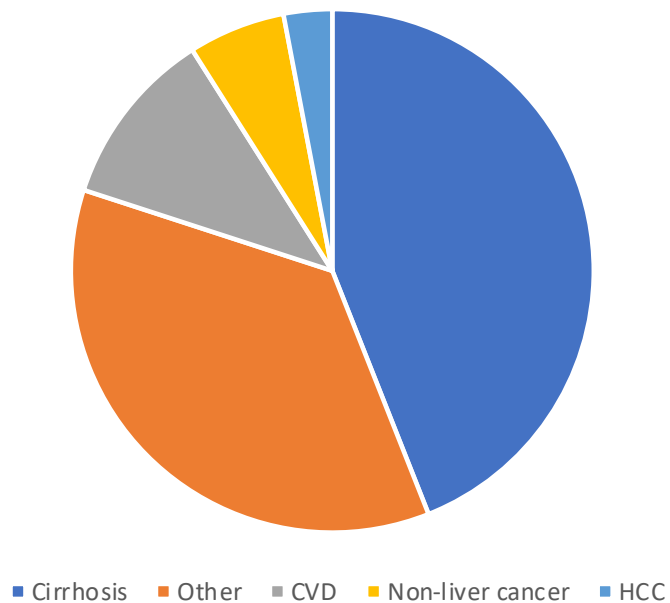


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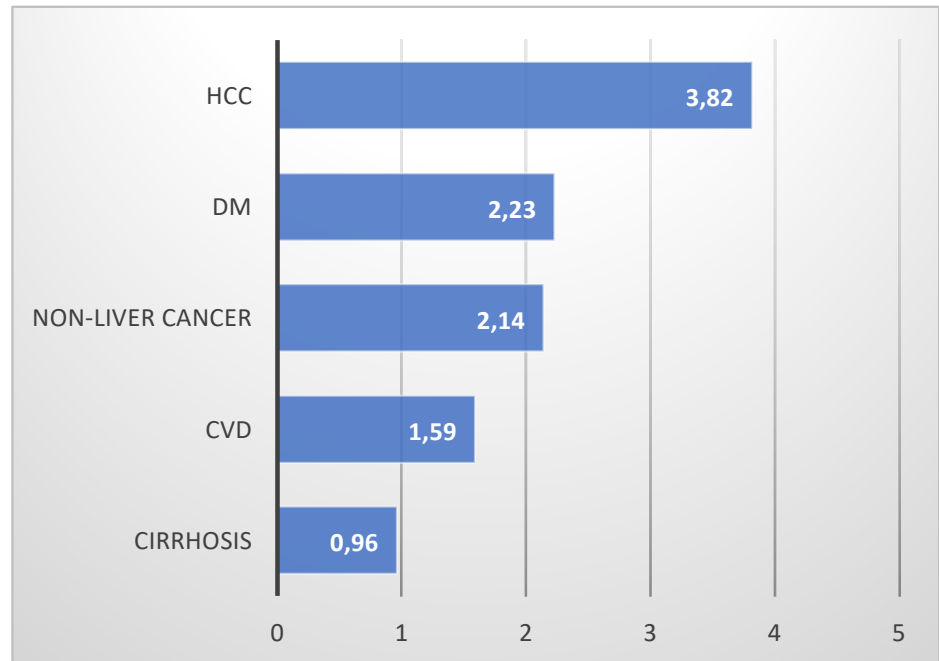


# Trend of mortality related to NAFLD

## Underlying Cause of Death



## Trend in % change in death rate





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# Agenda

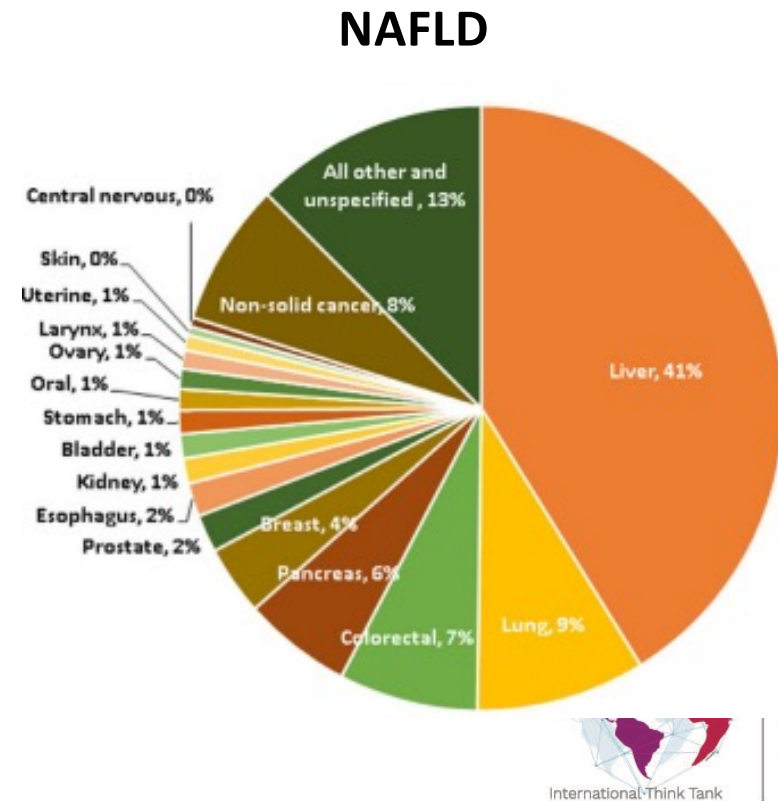
- Cancer mortality in NAFLD patients
- Which Cancers
- Clinical implications



# Percent distribution of cause of cancer death

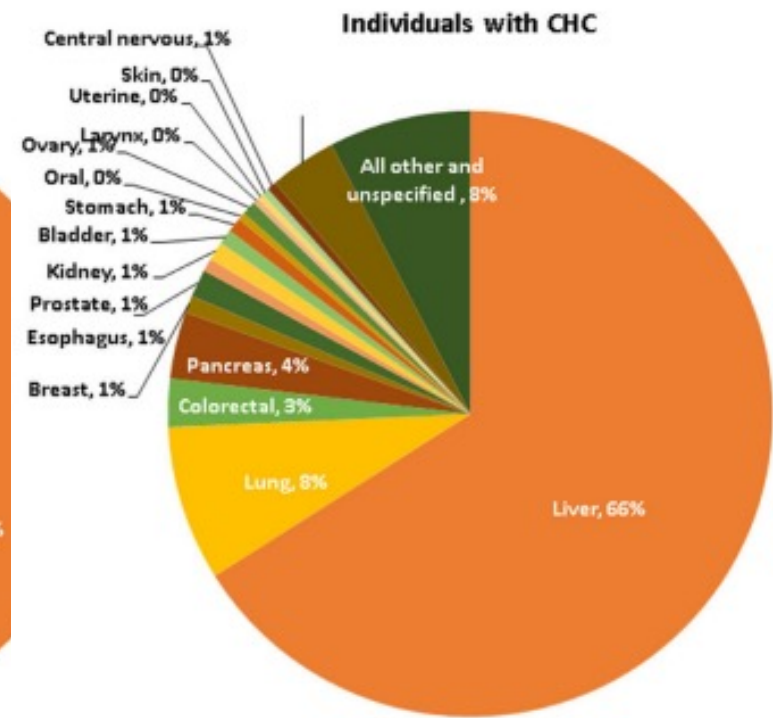
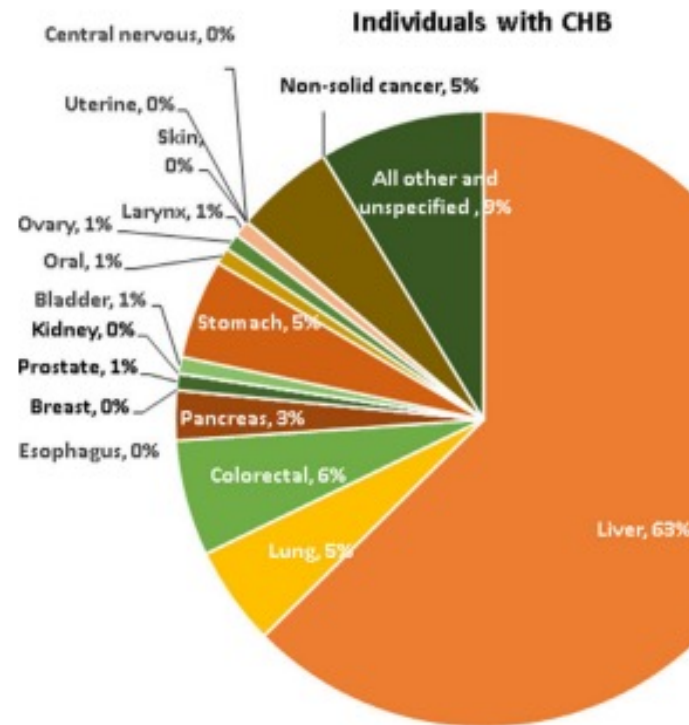
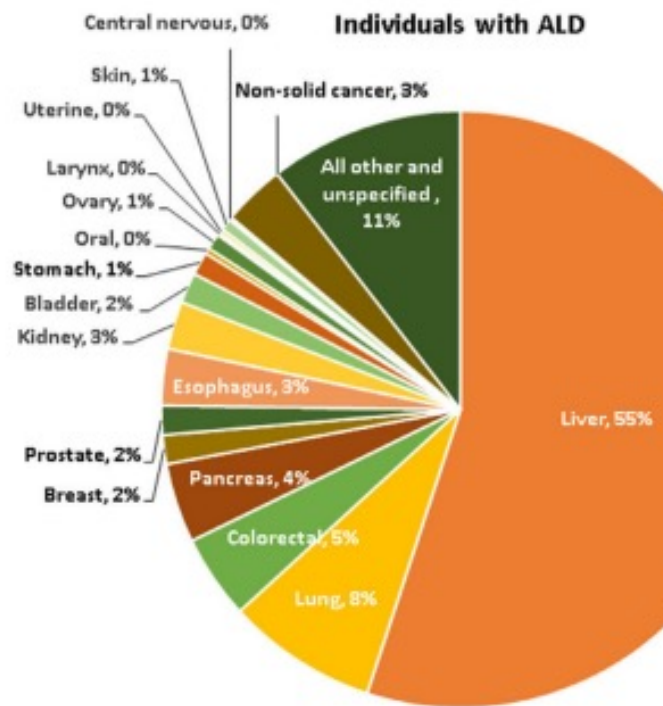
**Golabi al. Ann Hepatol 2022**

- Data from the US National Vital Statistics System (2008-2018)
- Cases with chronic liver disease and Cause-specific deaths identified by ICD codes



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# Percent distribution of cause of cancer death



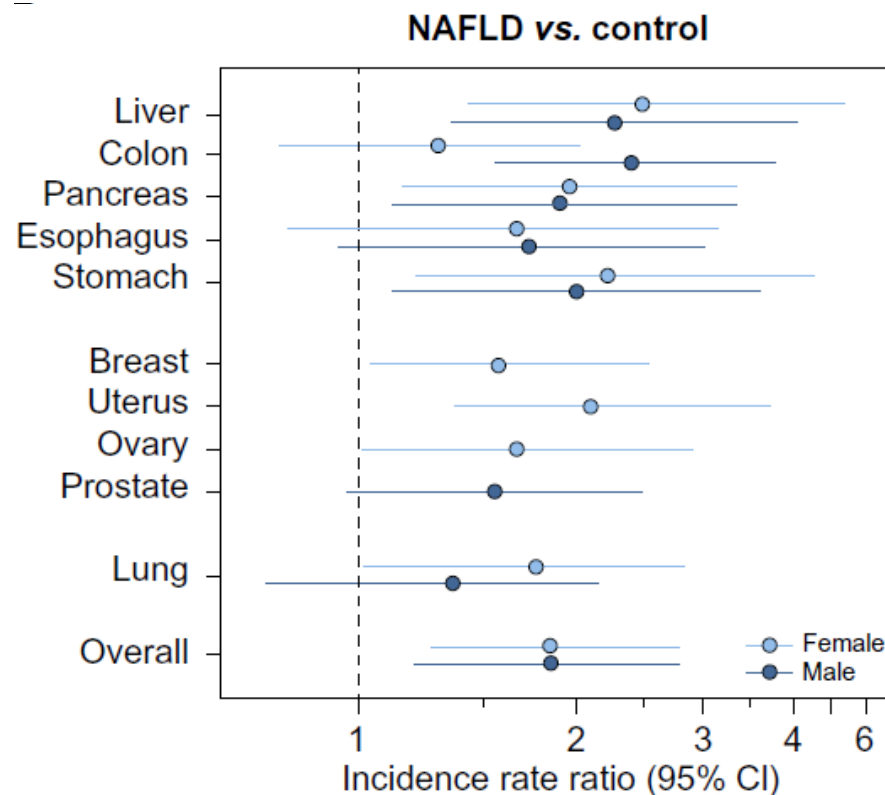
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# NAFLD and Cancer Incidence Rate

Allen al. J Hepatol 2019

- All 4722 incident cases of NAFLD in a US population between 1997-2016.
- NAFLD cases matched by age and sex to referent individuals from the same population (1:3).
- NAFLD and cancer defined using a code-based algorithm

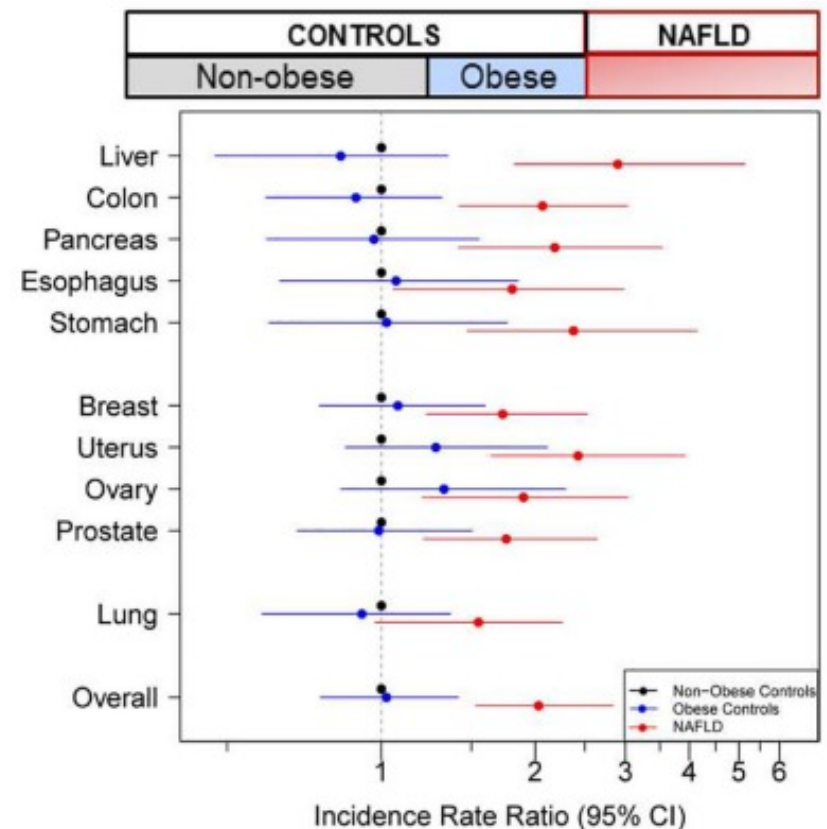




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# NAFLD and Cancer Incidence Rate

Retrospective Korean study 25,947 individuals over an average period of 7.5 years

	Number of cancers	Cancer incidence rate per 100,000 person-years				<i>P</i> -values
		All	NAFLD	No NAFLD	IRR	
<b>All cancers</b>	1,083	657.7	782.9	592.8	1.32	<0.001
<b>Colon/Rectum</b>	76	46.2	69.4	34.1	2.04	0.002
<b>HCC</b>	14	8.5	23.1	0.9	25.09	0.002
<b>Breast</b>	91	119.7	181.6	102.5	1.77	0.01

# NAFLD and Cancer Incidence Rate

Adjusted for age, gender, smoking status,  
diabetes, hypertension, GGT, HDL cholesterol,  
LDL cholesterol, and triglycerides

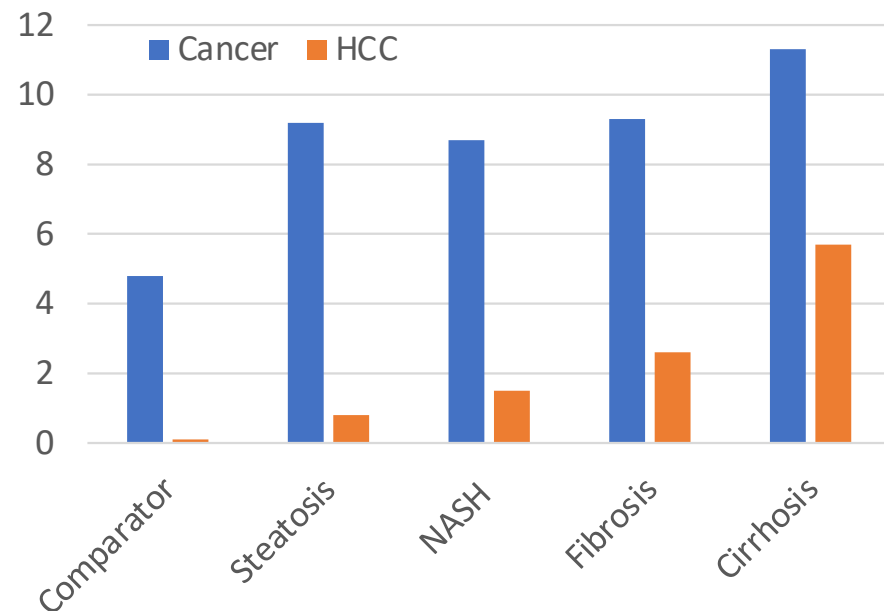
Multivariable analysis		
	HR (95% CI)	p value
FIB-4 score: Low, <1.45 (n = 7,007; reference), high and intermediate, ≥1.45 (n = 1,714)		
All cancers	1.74 (1.42–2.13)	<0.001
Hepatocellular carcinoma	13.99 (3.00–65.23)	0.001
Colon and rectum	1.64 (0.81–3.30)	0.17
Breast	1.80 (0.40–8.21)	0.45

# NAFLD as a risk factor for Cancer

## Simon et al. GUT 2021

- Matched cohort study of all individuals in Sweden with biopsy-confirmed NAFLD (1966–2017; n=10,568), after excluding other etiologies of liver disease.
- NAFLD cases were matched to general population comparators by age, sex, calendar year and county (n=49,925).

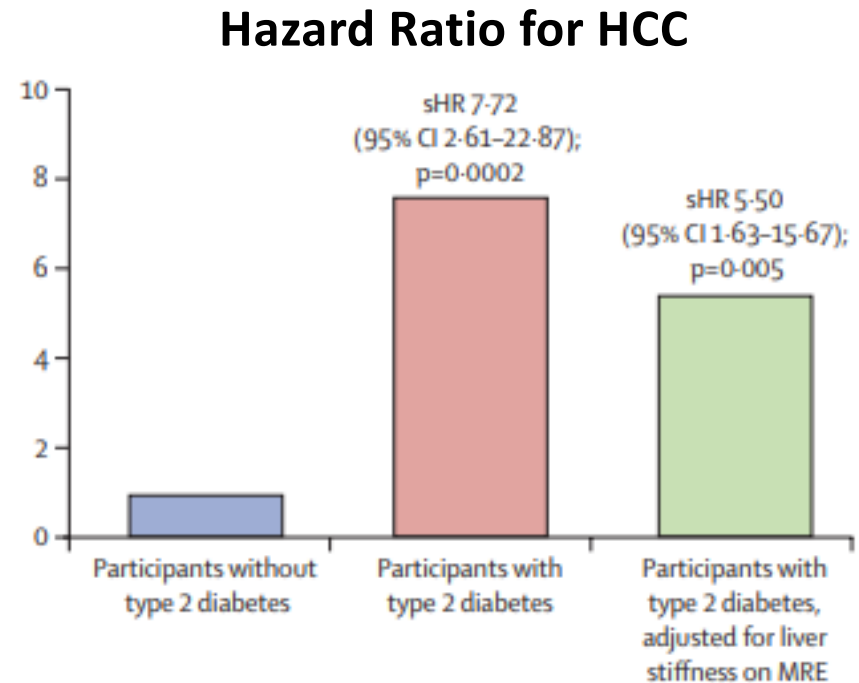
## Death, incidence rate par 1000 PY



# T2DM and risk of HCC in NAFLD patients

## Huang al. Lancet GastroHep 2023

- Meta-analysis of individual participant-level data from 6 cohorts (USA, Japan, and Turkey). Eligible cohorts :
  - Adult patients with NAFLD (Steatosis on imaging or Bx), for whom data were available regarding the presence of type 2 diabetes at baseline.
  - longitudinal assessment for hepatic decompensation and HCC
  - liver fibrosis characterisation by MRE

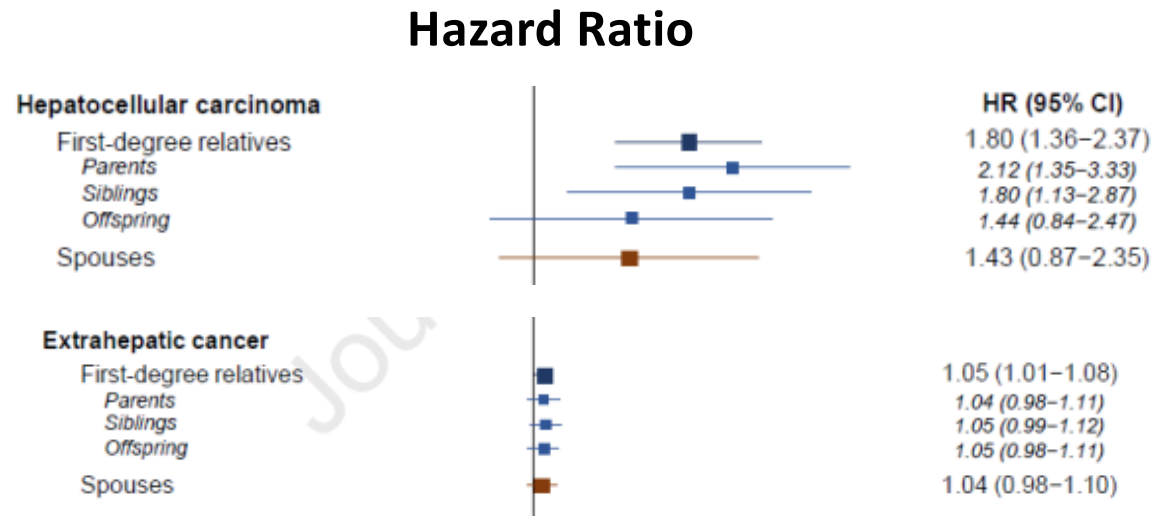




# Family as risk factor for Cancer in MASLD

Ebrahimi et al. J Hepatol 2023

- Nationwide Multi-Generation Cohort Study in Sweden
- FDR and spouses of Patients with biopsy-proven MASLD (n=47399)
- FDR and spouses of Matched Comparators (244875)
- Follow-up 17.6 years



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# Agenda

- Cancer mortality in NAFLD patients
- Which Cancers
- Clinical implications
  - Surveillance programs
  - Choice of treatment
  - Co-medication
  - Lifestyle intervention





# NAFLD patients in surveillance programs

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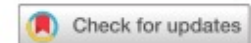
- Surveillance program for breast cancer
- Surveillance program for CRC
- Surveillance program for HCC



# Surveillance – emerging biomarkers

nature  
COMMUNICATIONS

ARTICLE



<https://doi.org/10.1038/s41467-020-17316-z>

OPEN

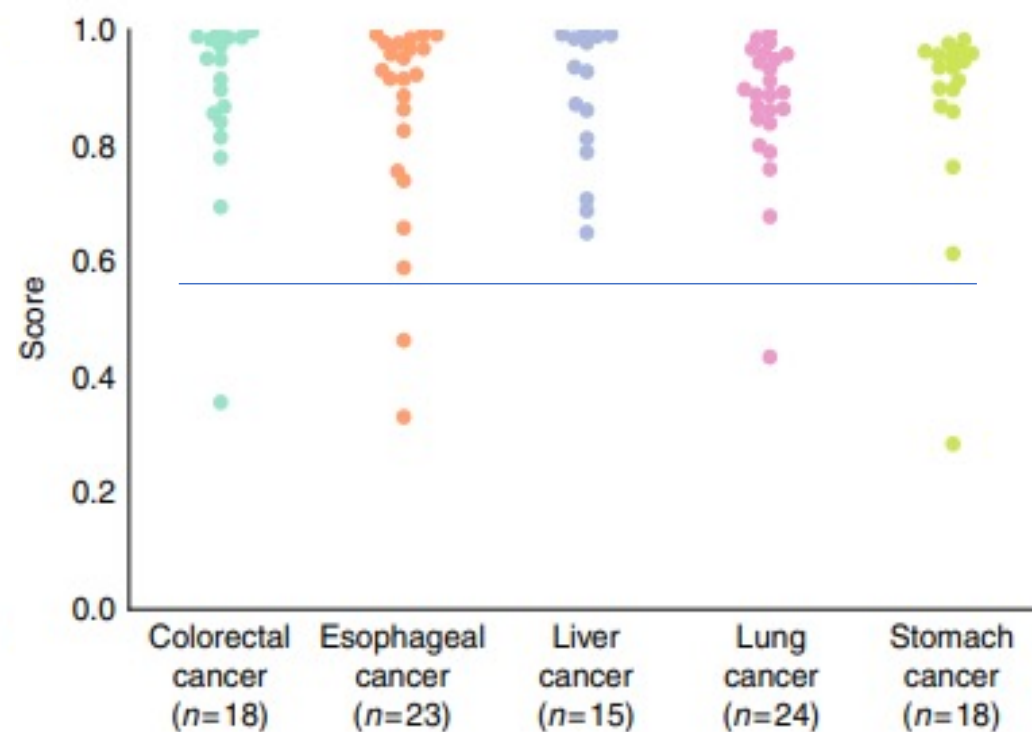
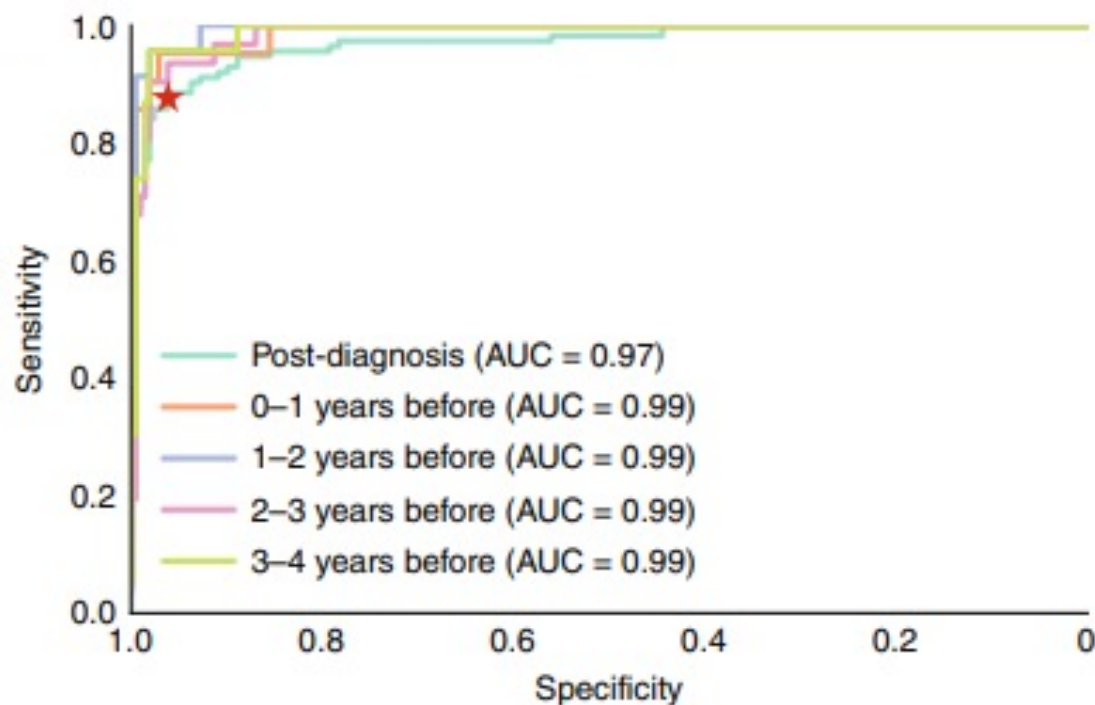
## Non-invasive early detection of cancer four years before conventional diagnosis using a blood test

Xingdong Chen<sup>1,2,3,12</sup>, Jeffrey Gole<sup>4,12</sup>, Athurva Gore<sup>4,12</sup>, Qiye He<sup>5,12</sup>, Ming Lu<sup>2,6,12</sup>, Jun Min<sup>4</sup>, Ziyu Yuan<sup>2</sup>, Xiaorong Yang<sup>2,6</sup>, Yanfeng Jiang<sup>1,2</sup>, Tiejun Zhang<sup>7</sup>, Chen Suo<sup>7</sup>, Xiaojie Li<sup>5</sup>, Lei Cheng<sup>5</sup>, Zhenhua Zhang<sup>5</sup>, Hongyu Niu<sup>5</sup>, Zhe Li<sup>5</sup>, Zhen Xie<sup>5</sup>, Han Shi<sup>4</sup>, Xiang Zhang<sup>8</sup>, Min Fan<sup>9</sup>, Xiaofeng Wang<sup>1,2</sup>, Yajun Yang<sup>1,2</sup>, Justin Dang<sup>4</sup>, Catie McConnell<sup>4</sup>, Juan Zhang<sup>2</sup>, Jiucun Wang<sup>1,2,3</sup>, Shunzhang Yu<sup>2,7</sup>, Weimin Ye<sup>2,10</sup>✉, Yuan Gao<sup>4</sup>✉, Kun Zhang<sup>10</sup>✉, Rui Liu<sup>4,5</sup>✉ & Li Jin<sup>1,2,3</sup>✉



# Surveillance – emerging biomarkers

PanSeer assay a noninvasive tests based on ctDNA methylation



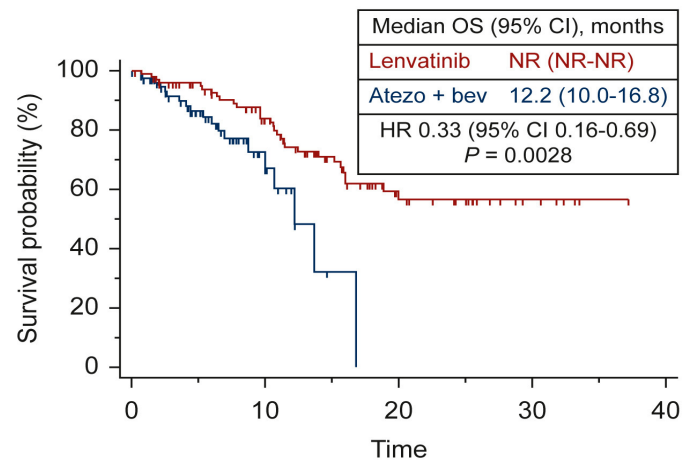
Chen *et al.*, Nature Comm 2020



# NAFLD & choice of HCC Treatment

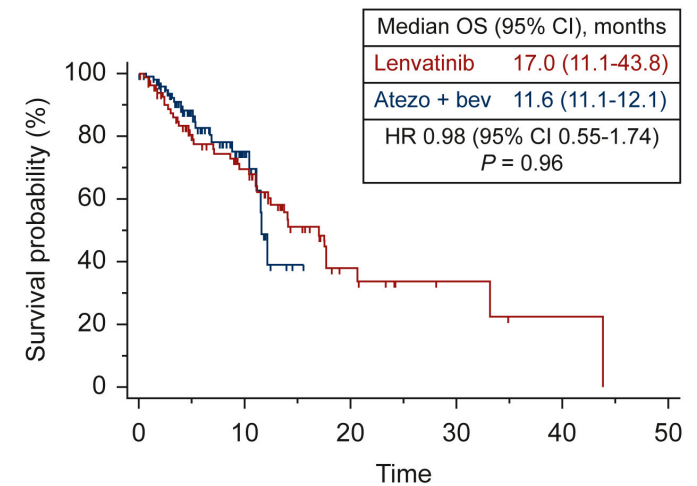
Atezo/Bev vs. Lenvatinib in unresectable HCC  
an international propensity score matching analysis

## Overall Survival, non-viral



Number at risk					
— Group: atezo + bev	81	11	0	0	0
— Group: lenvatinib	102	62	20	6	0

## Overall survival

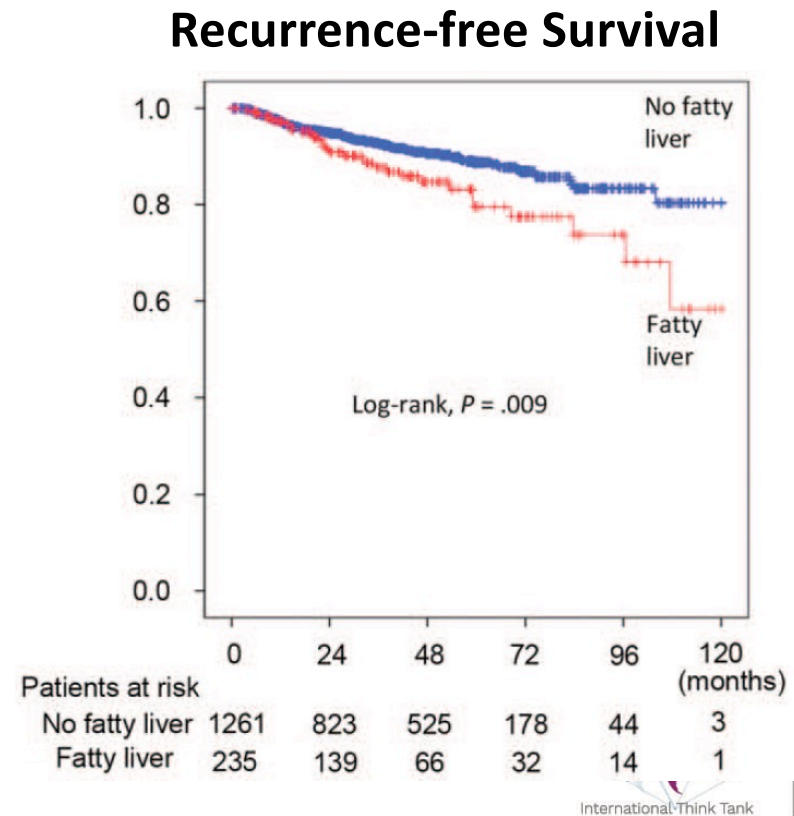


Number at risk						
— Group: atezo + bev	106	15	0	0	0	0
— Group: lenvatinib	85	42	9	3	1	0

# NAFLD & breast cancer recurrence after curative surgery

## Lee *et al.* Medicine 2019

- Korean retrospective analysis of 1949 newly diagnosed patients with breast cancer
- Fatty liver based on CT Scan



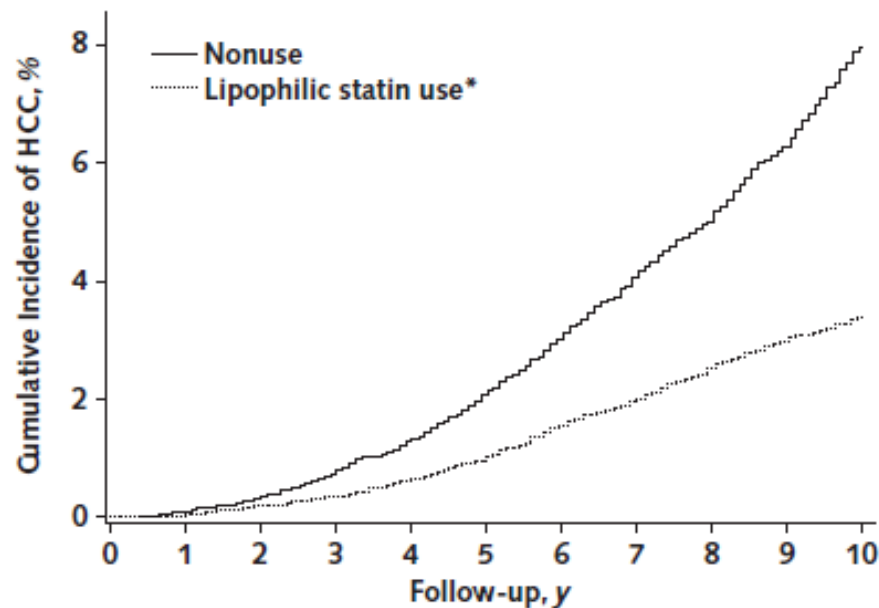


## Bariatric surgery & cancer risk in NAFLD patients

- Retrospective cohort study of newly diagnosed NAFLD patients with severe obesity between 2007 and 2017 (US MarketScan database)
- 98,090 patients were included in the study, 33,435 (34.1%) received bariatric surgery.
- Adjusted risk of any cancer was reduced by 18% (HR, 0.82; 95% CI, 0.76–0.89)
- Adjusted risk of obesity-related cancer was reduced by 25% (HR, 0.65; 95% CI, 0.56–0.75).
- Bariatric surgery was associated with significant risk reductions for colorectal, pancreatic, endometrial, thyroid cancers, HCC, and multiple myeloma.

# Statins and Cancer

Simon et al. Ann Int Med 2019



## Other Cancers

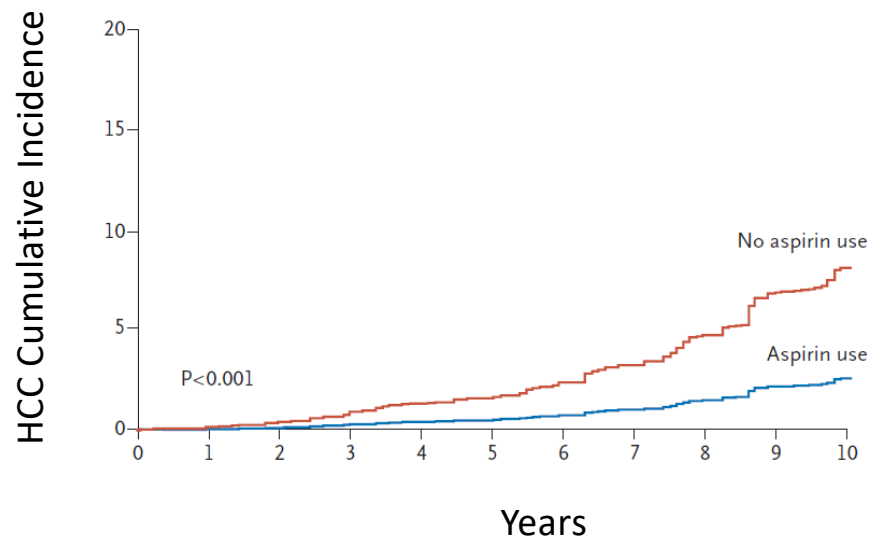
- Statins do not affect the incidence of most cancers
- Statins have significant benefit on cancer recurrence and survival in several cancer types including breast and CRC



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# Aspirin and HCC and Cancers

Simon et al. N Engl J Med 2020



Ricciotti & FitzGerald Ann Rev Med 2021,  
Ma et al. Clin Breast Cancer 2021

- Indirect evidence, both preclinical and clinical, suggests that aspirin protects against sporadic colorectal cancer.
- Meta-analysis : significant decrease in breast cancer risk with aspirin use (RR, 0.92; 95% CI, 0.89-0.96)



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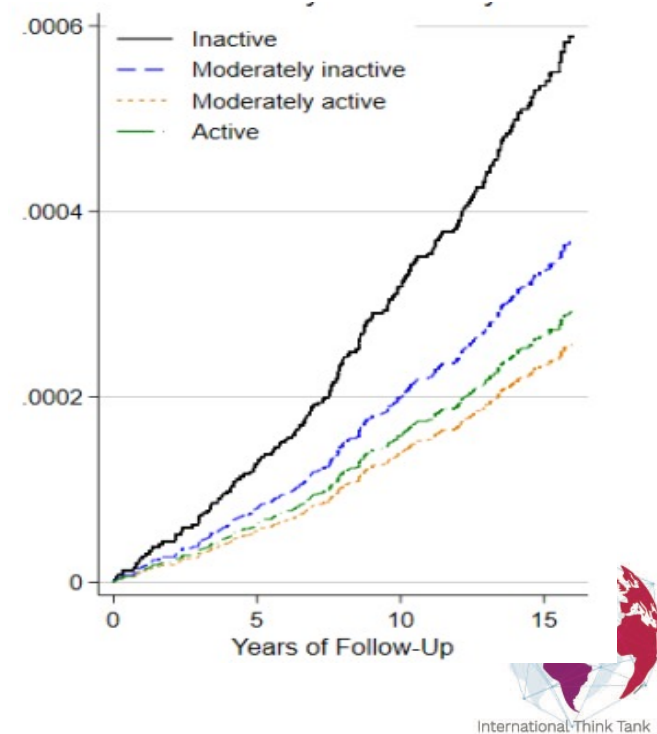


# Physical activity and HCC

**Baumeister *et al.* J Hepatol 2019**

- 275 HCC cases among 467,336 EPIC participants. Median follow-up 14.9 years.
- validated EPIC physical activity questionnaire (EPIC-PAQ)

**Cumulative Incidence of HCC**



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# Physical activity and cancers

	Effect of Physical Activity on Risk
Breast	↓
Colon	↓
Endometrium	↓
Kidney	↓
Lung	May ↓
Pancreas	May ↓
Ovary	May ↓

Rock et al. American Cancer Society Guidelines CA Cancer J Clin 2020



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# Cancer and NAFLD

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20% of NAFLD patients die of cancer.

NAFLD is associated with increased risk to develop cancers.

Extra-hepatic cancers(CR, breast, lung, pancreas) are more frequent than HCC.

Specific measures can be implemented regarding  
surveillance  
prevention.



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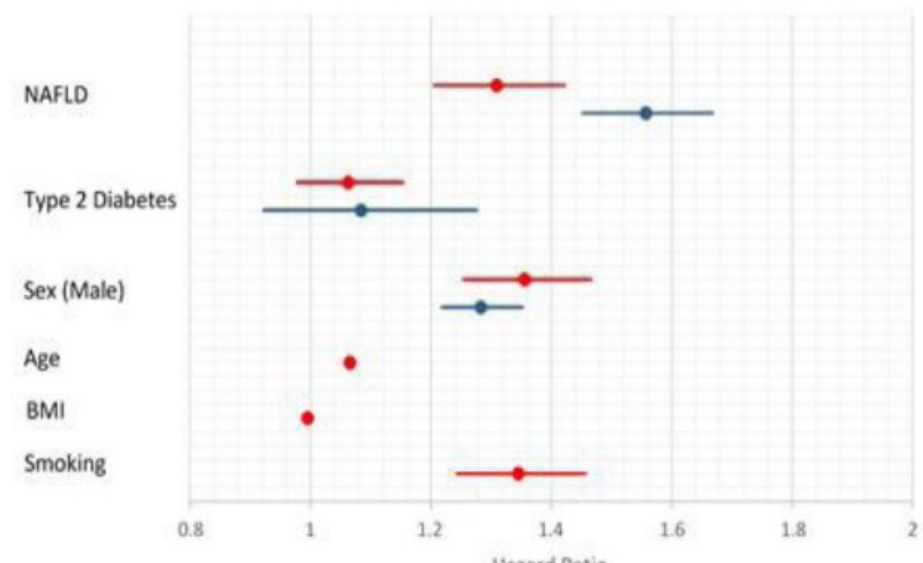


# NAFLD as a risk factor for Cancer

## Taylor al. BMJ Open Gastro 2022

- Retrospective analysis Scottish cohorts :
  - GoDARTS (case-control T2 DM, 13965, red)
  - SHARE (volunteers, 62438, blue).
- Metabolic Dysfunction related Liver Disease : ALT elevated twice, exclusion other causes

## Hazard Ratio for Cancer Incidence



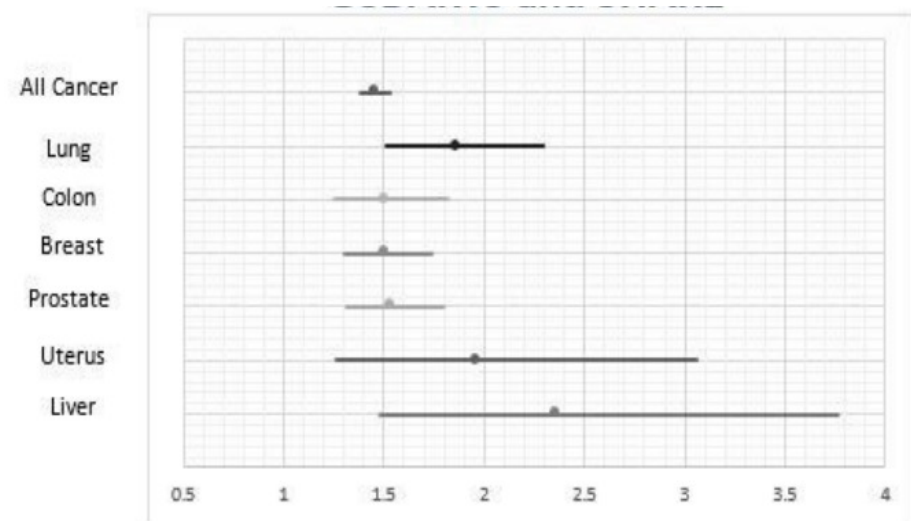
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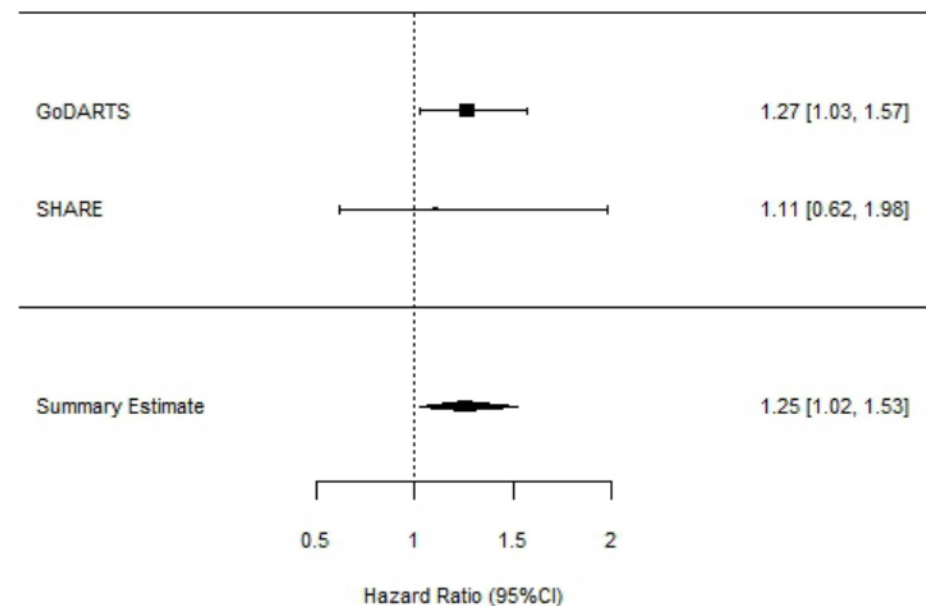
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## PNPLA3 Homozyg. & Cancer Incidence



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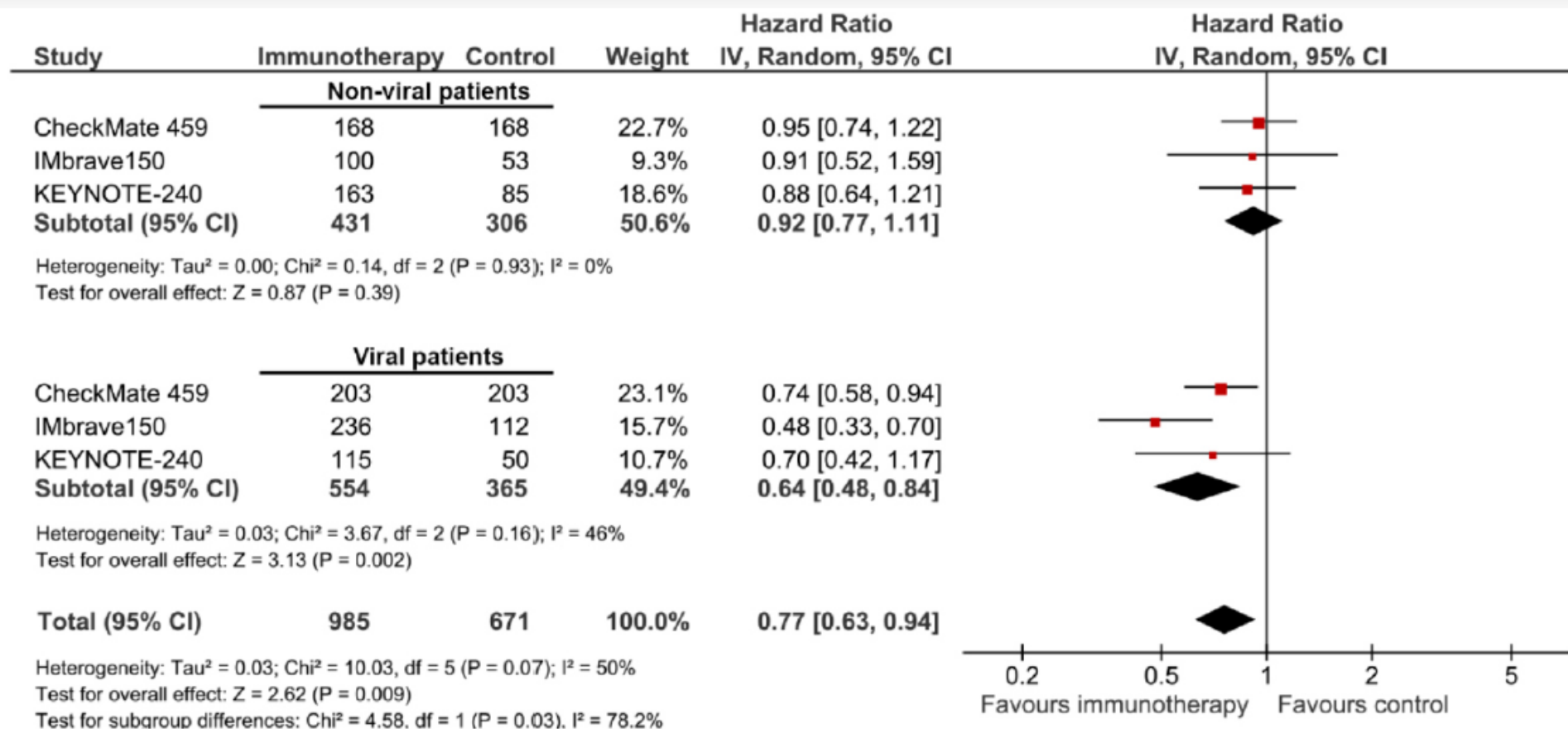




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Pfister *et al.* Nature 2021