Metabolic signatures of habitual alcohol intake and their association with gastrointestinal cancers in EPIC

Emeline Courtois[1,2], Marie Breeur[1], Erikka Loftfield[3], Pekka Keski-Rahkonen[1], Marc Gunter[4], Pietro Ferrari[1], Vivian Viallon[1]
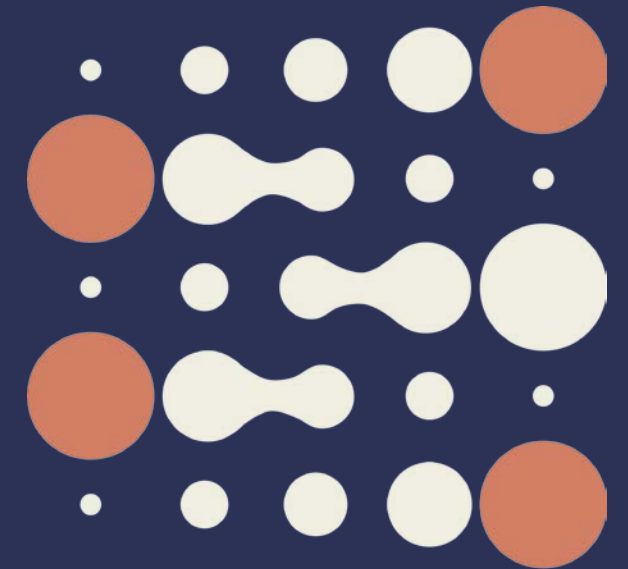
[1]*NME, IARC*
[2]*INSERM, Villejuif*
[3]*NCI*
[4]*Imperial College London*

breeurm@iarc.who.int

International Agency for Research on Cancer

World Health Organization

Background

- Established link between alcohol intake and gastrointestinal cancer
- Understanding of biological mechanisms still limited
- Untargeted Metabolomics to investigate this complex relationship

Example: Biomarker discovery in EPIC (Loftfield et al., 2021)

Exposure	Alcohol-adjusted models[b]	
	OR (95% CI)	P
HCC, EPIC (128 case-control sets)		
Unknown compound, 1-SD (log$_2$)[c]	1.23 (0.75 to 2.01)	.40
2-hydroxy-3-methylbutyric acid, 1-SD (log$_2$)[d]	3.12 (1.74 to 5.56)	4.2×10^{-4}
Pancreatic cancer, EPIC (152 case-control sets)		
Unknown compound, 1-SD (log$_2$)[c]	1.10 (0.83 to 1.46)	.50
2-hydroxy-3-methylbutyric acid, 1-SD (log$_2$)[d]	1.46 (1.03 to 2.06)	.03

- Our objective: construction of a metabolic signature of alcohol intake

Design

Data: Untargeted metabolomics data from 3 EPIC studies

- Cross-sectional (CS) study
- 2 nested cases-controls studies on hepatocellular carcinoma (HCC), and pancreatic cancer (PC)
- ➢ "Combining" metabolomics data : **CS+HCC+PC** datasets

	CS+HCC+PC
# samples	892
# features	704

1) Construction of the signature

On **controls data**, using **Lasso** regression and cross-validation.

Adjustment for age, sex, BMI, smoking status and intensity, coffee consumption, height, fasting status, physical activity, adherence to the Mediterranean diet without the alcohol component, and variables related to experimental conditions

2) Association with cancer

Conditional logistic regression

Adjustment for alcohol intake, BMI, coffee consumption, smoking intensity, physical activity, highest school level and adherence to the Mediterranean diet without the alcohol component

Results

Construction of the signature

➢ **20 features** selected in the signature (**including the 2-hydroxy-3-methylbutric-acid and the unknown compound** identified in Loftfield et al. 2021)

➢ Stronger correlation between signature and alcohol intake (**r=0.50**; 95%CI: 0.36-0.62) than with individual metabolites (< 0.4)

Association with cancer risk

Cancer type	HR (1SD)*	p-value
Hepatocellular carcinoma (HCC)	**1.61 [1.05 ; 2.47]**	**2.8e-02**
Pancreatic cancer (PC)	1.01 [0.68 ; 1.50]	0.93

* Adjusted for alcohol intake, BMI, coffee consumption, smoking intensity, physical activity, highest school level and adherence to the Mediterranean Diet *(without the alcohol component)*

Discussion and Conclusions

➢ Ongoing developments

  ➢ Assessment of the association between features comprising the signature and cancer risk

  ➢ Annotation of the features which comprise the signature

  ➢ Inclusion of data from the EPIC colorectal and breast cancer studies

  ➢ Findings to be consolidated in EPIC, and validated on independent observational and intervention studies

Key take-home messages

➢ Identification of a metabolic signature of alcohol consumption, associated with risk of hepatocellular carcinoma

➢ Metabolomics data provide a useful resource for investigating biological mechanisms possibly underlying the link between diet and cancer

➢ This framework will be applied to study other dietary exposures (dietary fibre, dairy products, coffee intake, …)

Project MeDiCa (WCRF); PI: V. Viallon (2023-2026)

Features identified in the signature

136.0624@0.6207057

175.1205@0.76103795

118.0098@0.7656218

184.0326@0.7767216

230.0766@0.89200854

166.0499@0.9115857

216.9822@2.7771502

125.0470@2.8166192

325.0249@3.2127516

262.1199@5.290392

285.1378@5.991719

481.3153@6.8887777

268.2197@7.225316

409.2497@8.417876

743.5448@8.512558

731.5455@8.606333

801.0397@8.668163

781.5645@8.672886

781.0500@8.702749

759.5758@9.108256