Association between Per- and Polyfluoroalkyl Substances and Liver Cancer Risk

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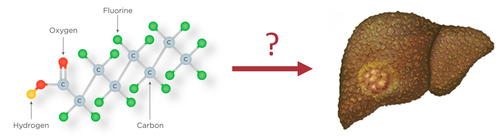
INTRODUCTION

- Liver cancer incidence in the US has tripled since the 1980s.
- The underlying causes likely include exposures to hepatotoxic environmental contaminants, e.g., per- and polyfluoroalkyl substances (PFAS).
- PFAS are highly cumulative in human liver tissue and associate with higher risk of metabolic dysfunction-associated steatotic liver disease (MASLD) .

AIMS

To study prospectively the circulating levels of PFAS in nested case-control studies comparing liver cancer cases with:

- Generally healthy individuals (**Aim 1**)
- Individuals with MASLD (**Aim 2**).



AIM 1. To examine pre-diagnosis blood PFAS in 44 pairs of liver cancer cases and cancer/liver disease-free controls.

METHODS

- A nested case-control study based on the Women's Health Study (WHS) and the Physicians' Health Study (PHS) I and II
- Primary liver cancer is verified by medical record review
- 1:1 cancer-free control matched by age, sex, and blood collection year
- PFAS measured in archived pre-diagnosis blood samples (baseline year 1993–1995 in WHS, 1982 in PHS I, and 1997 in PHS II)
- Conditional logistic regression analysis, further adjusted for potential confounders

RESULTS

Table 1. Baseline characteristics of selected participants in the WHS and PHS.

	Liver cancer, N=44	Control, N=44	*P*
Age, year	61.1 (10.2)	61.0 (10.2)	0.97
Sex, n (%)			N/A
Female (WHS)	28 (63.6)	28 (63.6)	
Male (PHS)	16 (36.4)	16 (36.4)	
Non-Hispanic white, n (%)	40 (90.9)	41 (93.2)	0.69
Current smoker, n (%)	20 (45.5)	21 (47.7)	0.83
1+ alcoholic drink/week, n (%)	26 (59.1)	21 (47.7)	0.29
1+ time/week vigorous physical activity, n (%)	24 (54.6)	24 (54.6)	>0.99
Body mass index (BMI), kg/m^2	25.9 (4.4)	25.5 (3.3)	0.63
Type 2 diabetes mellitus (T2DM), n (%)	5 (11.4)	1 (2.3)	0.09
High cholesterol, n (%)	12 (27.3)	15 (34.1)	0.49
Current postmenopausal hormone (in women), n (%)	17 (60.7)	11 (39.3)	0.11

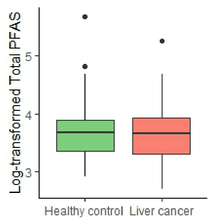


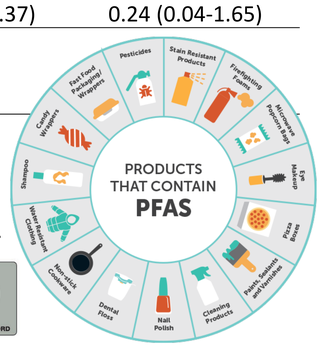
Figure 1. Boxplot of log-transformed total PFAS level by case control status.

- **Perfluorodecanoic acid (PFDA)** and **perfluoroundecanoic acid (PFUnDA)** at high levels (>=90th percentile) might be associated with liver cancer risk

Table 2. Conditional logistic regression analysis for total and individual PFAS and liver cancer risk.

	Tertile 1	Tertile 2 vs. 1	Tertile 3 vs. 1	90th percentile, above vs. below
Total PFAS				
Median (range), ng/mL	24.7 (14.9-32.4)	39.1 (33.1-49.0)	57.6 (49.0-291.8)	>=65.0
Case/control N	15/14	13/17	16/13	4/5
Crude OR (95% CI)	1 (ref.)	0.71 (0.24-2.09)	1.13 (0.38-3.40)	0.60 (0.14-2.51)
Adjusted OR (95% CI)†	1 (ref.)	0.76 (0.19-2.99)	1.09 (0.28-4.28)	0.29 (0.04-1.93)
PFHxS	1 (ref.)	0.79 (0.24-2.65)	1.20 (0.38-3.77)	1.29 (0.27-6.16)
PFHpA	1 (ref.)	0.34 (0.08-1.41)	0.41 (0.09-1.90)	0.12 (0.01-1.51)
PFHpS	1 (ref.)	0.55 (0.17-1.78)	0.76 (0.18-3.15)	1.15 (0.23-5.78)
FOSA	1 (ref.)	0.31 (0.08-1.26)	0.45 (0.10-1.95)	Not estimated
PFOA	1 (ref.)	0.22 (0.05-0.92)	0.29 (0.06-1.37)	0.32 (0.05-1.97)
PFOS	1 (ref.)	1.00 (0.27-3.76)	1.30 (0.34-5.02)	0.33 (0.05-1.96)
PFNA	1 (ref.)	0.21 (0.04-1.25)	0.96 (0.25-3.70)	3.48 (0.53-23.0)
PFDA	1 (ref.)	0.61 (0.16-2.37)	1.54 (0.38-6.16)	7.96 (1.09-58.4)
PFDS	1 (ref.)	1.03 (0.27-3.93)	2.12 (0.58-7.77)	0.96 (0.20-4.53)
PFUnDA	1 (ref.)	0.52 (0.13-2.06)	1.62 (0.40-6.47)	10.5 (1.06- 103)
N_EtFOSAA	1 (ref.)	0.60 (0.15-2.34)	0.56 (0.13-2.37)	0.24 (0.04-1.65)

† Stratified by matching pairs (age, sex, time of blood draw) and adjusted for ethnicity, smoking status, alcohol intake, physical activity, BMI, T2DM, high cholesterol, and postmenopausal hormone (in women).



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AIM 2. To examine pre-diagnosis blood PFAS in 66 pairs of liver cancer cases and MASLD controls.

METHODS

- A case-control study based on the Mass General Brigham Biobank, a hospital collection of research data and sample repository.
- Primary liver cancer and MASLD are identified based on ICD-codes
- 1:1 cancer-free MASLD control matched by age, sex, ethnicity, and blood collection year.
- PFAS measured in archived pre-diagnosis blood samples (median year 2014).
- Conditional logistic regression analysis, further adjusted for potential confounders

RESULTS

Table 3. Baseline characteristics of selected participants in the Mass General Brigham Biobank.

	Liver cancer, N=66	MASLD control, N=66	*P*
Age, year	59.8 (11.9)	60.1 (11.9)	0.98
Sex, n (%)			N/A
Female	21 (31.3)	21 (31.3)	
Male	46 (68.7)	46 (68.7)	
Non-Hispanic white, n (%)	56 (83.6)	56 (83.6)	N/A
Current smoker, n (%)	10 (14.9)	11 (16.4)	0.82
Current alcohol drinker, n(%)	27 (40.3)	37 (55.2)	0.07
Body mass index, kg/m^2	29.9 (5.8)	33.4 (7.3)	<.001
Type 2 diabetes mellitus, n (%)	30 (44.8)	36 (53.7)	0.57
Hepatitis B virus infection, n (%)	3 (4.5)	1 (1.5)	<.001
Hepatitis C virus infection, n (%)	18 (26.9)	0	N/A

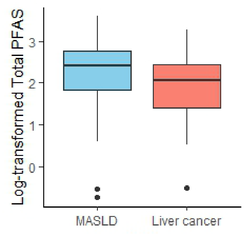

Figure 2. Boxplot of log-transformed total PFAS level by case and liver disease control status.

- Compared to MASLD controls, adjusted models did not show statistically significant associations; there is a trend towards higher MASLD risk with higher PFAS levels

Table 4. Conditional logistic regression analysis for total and individual PFAS and liver cancer risk.

	Tertile 1	Tertile 2 vs. 1	Tertile 3 vs. 1	90th percentile, above vs. below
Total PFAS				
Median (range), ng/mL	3.62 (0.48, 6.60)	8.61 (6.63, 12.0)	16.7 (12.1, 36.1)	>=18.5
Case/control N	26/18	25/19	15/29	7/11
Crude OR (95% CI)	1 (ref.)	0.76 (0.30-1.95)	0.31 (0.11-0.84)	0.56 (0.19-1.66)
Adjusted OR (95% CI)¶	1 (ref.)	0.95 (0.30-2.99)	0.23 (0.04-1.15)	0.36 (0.04-3.51)
PFHxS	1 (ref.)	0.98 (0.29-3.31)	0.40 (0.09-1.71)	0.52 (0.09-2.86)
PFHpA	1 (ref.)	0.94 (0.21-4.27)	0.59 (0.13-2.65)	0.63 (0.15-2.73)
PFHpA	1 (ref.)	0.94 (0.21-4.27)	0.59 (0.13-2.65)	0.63 (0.15-2.73)
PFHpS	1 (ref.)	1.26 (0.36-4.35)	0.61 (0.13-2.76)	0.29 (0.03-2.91)
PFOA	1 (ref.)	0.57 (0.12-2.79)	0.77 (0.21-2.85)	Not estimated
PFOS	1 (ref.)	0.96 (0.29-3.22)	0.33 (0.07-1.47)	0.66 (0.11-4.02)
PFNA	1 (ref.)	0.24 (0.04-1.38)	0.38 (0.10-1.50)	Not estimated
PFDA	1 (ref.)	1.05 (0.28-3.91)	0.13 (0.01-1.07)	0.54 (0.05-6.03)
PFUnDA	1 (ref.)	0.91 (0.22-3.80)	0.32 (0.07-1.41)	1.93 (0.17-21.9)

¶ Stratified by matching pairs (age, sex, ethnicity, time of blood draw) and adjusted for, smoking status, alcohol intake, BMI, T2DM, and hepatitis B/C virus infection.

CONCLUSIONS

- In both studies, overall, we did not find consistent significant associations between total or individual PFAS and liver cancer risk
- Certain PFAS at high levels might be associated with higher liver cancer risk compared to non-cancer healthy status, although evidence from larger scale studies is warranted
- PFAS hepatoxicity may manifest in earlier stages of liver disease, e.g., MASLD
- Limitations: (1) single PFAS assessment, (2) small sample sizes and multiple testing
- Future directions: (1) longitudinal change in PFAS, (2) joint effects of PFAS mixtures (e.g., weighted quantile sum regression, quantile G-computation, and Bayesian Kernel Machine Regression), (3) PFAS and liver disease