

Table S1. Spearman correlations between OPN levels and AFP, CRP or liver function markers among HCC Cases and among Controls.

	Spearman correlation with OPN, ng/ml			
	Controls (n=194)		HCC cases (n=100)	
	R	p-value	R	p-value
AFP, ng/ml	-0.02	0.829	0.24	0.022
CRP, mg/l	0.12	0.107	0.38	<0.001
ALT, U/l	-0.21	0.004	-0.02	0.818
AST, U/l	-0.13	0.074	0.21	0.039
GGT, U/l	-0.06	0.371	0.25	0.014
ALP, U/l	0.06	0.418	0.36	<0.001
Albumin, g/l	-0.37	<.0001	-0.48	<0.001
Total bilirubin, μ mol/l	-0.02	0.810	0.12	0.237

Spearman correlation coefficients were adjusted for age at recruitment and sex.

Table S2. Odds ratios (OR) and 95% confidence intervals [95% CI] of hepatocellular carcinoma per 10% increase in circulating OPN levels (ng/ml)^a in the EPIC nested case-control study.

Model	N° HCC cases	OPN mean (SD), median (ng/ml)	OR [95% CI]^b
All data	100	66.5 (61.7), 56.0	1.30 [1.14-1.48]
Additionally adjusted for			
AFP, ng/ml	100	-	1.19 [1.05-1.35]
BARD score	100	-	1.30 [1.14-1.48]
AST/ALT ratio	100	-	1.29 [1.14-1.48]
ALT, U/l	100	-	1.25 [1.08-1.43]
AST, U/l	100	-	1.19 [1.02-1.38]
GGT, U/l	100	-	1.25 [1.07-1.46]
ALP, U/l	100	-	1.18 [1.02-1.37]
Albumin, g/l	100	-	1.21 [1.06-1.38]
Total bilirubin, µmol/l	100	-	1.26 [1.11-1.44]
HBV/HCV status	100	-	1.26 [1.11-1.43]
Stratified analyses			
By sex			
Men	70	70.0 (71.9), 57.2	1.44 [1.19-1.74]
Women	30	58.3 (23.9), 54.4	1.07 [0.87-1.32]
By years of follow-up			
< 2 y	21	144.8 (199.6), 69.9	2.51 [1.06-5.95]
2-6 y	40	70.8 (32.8), 59.5	1.45 [1.13-1.85]

> 6 y	39	58.1 (23.5), 54.0	1.05 [0.89-1.24]
By viral hepatitis status			
HBV/HCV positive	27	64.1 (20.8), 59.4	2.45 [1.24-4.83]
HBV/HCV negative	70	67.1 (66.2), 55.2	1.19 [1.05-1.34]
Sensitivity analyses			
AFP < 20 ng/ml	87	64.1 (55.0), 55.2	1.24 [1.10-1.41]
AFP < 10 ng/ml	75	63.7 (56.5), 54.5	1.23 [1.09-1.41]
Non-diabetic	80	68.2 (66.5), 56.4	1.40 [1.18-1.66]

^a OPN levels correspond to a 10% increment after log transformation.

^b ORs and 95% CIs estimated by conditional logistic regression conditioned on the matching factors and adjusted for body mass index (kg/m², continuous), smoking status (never, former, current, unknown), baseline alcohol intake (g/d, continuous), and lifetime alcohol intake pattern (never drinkers, former drinkers, drinkers only at recruitment, lifetime drinkers, unknown).

Table S3: Random repeated assignment of cases and their matched controls to classifier calibration (80% of subjects) and classifier validation (remainder 20% of subjects) components.

	Classifier calibration AUC [95%CI]	Classifier validation AUC [95% CI]
SAMPLE SET 1		
OPN	0.71 [0.64-0.79]	0.67 [0.52-0.81]
AFP	0.77 [0.70-0.83]	0.74 [0.60-0.89]
OPN+AFP	0.79 [0.73-0.86]	0.73 [0.59-0.86]
OPN+liver enzymes	0.86 [0.80-0.92]	0.85 [0.73-0.97]
OPN+AFP+liver enzymes	0.87 [0.81-0.93]	0.84 [0.73-0.96]
SAMPLE SET 2		
OPN	0.69 [0.62-0.76]	0.76 [0.61-0.90]
AFP	0.78 [0.71-0.84]	0.71 [0.56-0.85]
OPN+AFP	0.79 [0.72-0.85]	0.78 [0.64-0.93]
OPN+liver enzymes	0.86 [0.80-0.92]	0.82 [0.70-0.94]
OPN+AFP+liver enzymes	0.87 [0.81-0.92]	0.78 [0.64-0.91]
SAMPLE SET 3		
OPN	0.72 [0.65-0.79]	0.64 [0.48-0.80]
AFP	0.75 [0.68-0.82]	0.82 [0.72-0.93]
OPN+AFP	0.78 [0.71-0.85]	0.83 [0.72-0.93]
OPN+liver enzymes	0.87 [0.81-0.92]	0.93 [0.86-1.00]
OPN+AFP+liver enzymes	0.87 [0.82-0.92]	0.93 [0.85-1.00]
SAMPLE SET 4		
OPN	0.70 [0.63-0.78]	0.69 [0.52-0.86]
AFP	0.75 [0.69-0.82]	0.79 [0.65-0.92]
OPN+AFP	0.78 [0.72-0.85]	0.79 [0.66-0.92]
OPN+liver enzymes	0.85 [0.79-0.91]	0.90 [0.80-1.00]
OPN+AFP+liver enzymes	0.86 [0.80-0.91]	0.91 [0.82-1.00]
SAMPLE SET 5		
OPN	0.70 [0.62-0.77]	0.74 [0.61-0.87]
AFP	0.77 [0.70-0.83]	0.76 [0.62-0.89]
OPN+AFP	0.78 [0.71-0.84]	0.83 [0.73-0.94]
OPN+liver enzymes	0.86 [0.80-0.92]	0.85 [0.75-0.96]
OPN+AFP+liver enzymes	0.86 [0.80-0.92]	0.88 [0.78-0.97]
Average		
OPN	0.71	0.70
AFP	0.76	0.76
OPN+AFP	0.78	0.79
OPN+liver enzymes	0.86	0.87

OPN+AFP+liver enzymes

0.86

0.87