Table 3. Cohort studies of screening for hepatocellular carcinoma in patients with chronic liver disease

Author, Year, Setting, Years of enrollment	Screening modality, frequency (months); N screening vs no screening	Demographics (age; % male; race) Etiology, %	Etiology, %	Liver disease severity, %	Stage at Diagnosis, %	Treatment received, %	Observed mortality, screening vs no screening	Adjusted mortality, screening vs no screening
Bolondi, 2001[32] Europe: Italy 1989-1991	US+AFP, 6 313 vs 104	age: 61.8 vs 63.8 male: 70.5 vs 67.3	screening group only: HBV: 17.6 HCV: 64.2 Alcohol: 25.2 Primary biliary cirrhosis: 3.2	Child-Pugh: A: 41.0 vs 38.5 B: 47.5 vs 49.0 C: 11.5 vs 12.5	Unifocal HCC: 80 vs 53, p<0.001 Diffuse/ infiltrative HCC: 10 vs 29, p<0.01	Resection: 9 vs 8 OLT: 26 vs 13, p<0.01 PEI: 24 vs 23 TACE+PEI: 10 vs 10 TACE: 31 vs 46, p<0.05	Median survival (m) 30 vs 15 (p<0.02) Survival (%) at 3yr: 45 vs 31.7	*
Chen, 2002[33] Asia: Taiwan 1991-1998	US, 3-12 4385 vs 458	age ≥ 50: 45.0 vs 43.3 male: 78.7 vs 59.8	HBV: 65.9 vs 67.0 HCV: 18.2 vs 14.9	NR, but only 7 had cirrhosis	NR	NR	Unadjusted HR 0.76 (95% CI 0.38-1.52)	Adjusted[a] HR 0.59 (95% CI 0.29-1.20)
Davila, 2007[34] U.S - 3 VAMCs (Houston, Tennessee Valley, Kansas City) 1998-2003	AFP, US, or CT, within 36mo of HCC diagnosis 44 vs 113	age <65: 77.3 vs 55.8 (p=0.01) age ≥ 65: 22.7 vs 44.3 white: 68.1 vs 55.8	HBV: 6.8 vs 8.0 HCV: 72.7 vs 47.8 ETOH: 40.9 vs 14.2	Child-Pugh: A: 15.9 vs 26.5 B: 52.3 vs 35.4 C: 31.8 vs 38.1	One mass: 52.3 vs 38.1 2-3 masses: 22.7 vs 27.4 >3 masses: 18.2 vs 22.1	treatment n=54: Resection: 18.5 RFA: 11.1 PEI: 1.9 TACE: 35.2 chemotherapy: 31.5	Survival (%) at 1yr: 39 vs 31 3yr: 30 vs 21 (p=0.07)	*
El-Serag, 2011[35] U.S. (national VA HCV registry) 1998-2007	US and/or AFP, within 24mo of HCC diagnosis 1148 vs 332	age: 58.1 male: 99.3 white: 55.6	HCV:100	NR (but measured)	NR	NR	Unadjusted HR (95% CI) from date of HCC diagnosis, by timeframe screened during 24m prior to HCC diagnosis: 7-24m: 0.84 (0.69-1.01) 0-6m: 0.80 (0.68-0.94) Both periods: 0.71 (0.62-0.82) Median survival (days) from date of HCC diagnosis among pts screened in both periods vs neither: 368 vs 130 (p<0.01) Unadjusted HR (95% CI) from date of HCV diagnosis: 7-24m: 0.86 (0.72-1.04) 0-6m: 0.90 (0.77-1.06) Both periods: 0.82 (0.72-0.95) Median survival (days) from date of HCV diagnosis among pts screened in both periods vs neither: 1951 vs 1782	Adjusted[b] HR (95% CI) by timeframe screened during 24m prior to HCC diagnosis: 7-24m: 0.93 (0.77-1.13) 0-6m: 0.93 (0.79-1.09) Both periods: 0.84 (0.72-0.98) Adjusted HR corrected for lead time, assuming HCC sojourn time of 140 days: 7-24m: 1.04 (0.87-1.26) 0-6m: 1.00 (0.85-1.17) Both periods: 0.88 (0.76-1.02)
Giannini, 2000[36] Europe: Italy 1993-1998	AFP+US, 6 34 vs 27	age: 67 vs 68	HCV: 100	Mean Child-Pugh: 6 vs 8	One mass: 58.8 vs 51.9 >2 masses: 41.2 vs 48.5	Resection: 11.8 vs 7.4 OLT: 2.9 vs 0 PEI: 52.9 vs 33.3 TACE: 29.4 vs 25.9 None: 2.9 vs 33.3	Median survival (m) 23 vs 15 (p=0.03)	Adjusted[c] HR 0.38 (95% CI 0.17-0.87)

Author, Year, Setting, Years of enrollment	Screening modality, frequency (months); N screening vs no screening	Demographics (age; % male; race) Etiology, %	Etiology, %	Liver disease severity, %	Stage at Diagnosis, %	Treatment received, %	Observed mortality, screening vs no screening	Adjusted mortality, screening vs no screening
Kemp, 2005[37] Hospital, Victoria, Australia 1994-2002	US, 6-12 +AFP, 6 41 vs 55	age: 65 vs 68 male: 88.0 vs 78.2 Asian: 14.6 vs 16.7	HBV: 26.8 vs 12.9 HCV: 39.0 vs 29.6 Alcohol use: 43.9 vs 37.0	Child-Pugh: A: 63 vs 42 B: 27 vs 33 C: 10 vs 25	TNM I/II: 61.1 vs 21.7 III/IV: 38.9 vs 78.3, p<0.001	Resection: 11.8 vs 6.8 PEI or RFA: 52.9 vs 6.8 TACE: 33.0 vs 13.0	Median survival (m) 29.0 vs 3.3 (p<0.001)	Adjusted[d] HR 0.24 (p<0.0005)
Kuo, 2010[38] Asia: Taiwan 2002-2004	AFP+US, 12 318 vs 1118	age: 59.7 vs 59.4 male: 67.6 vs 76.4 (p=0.002)	HBV: 48.7 vs 47.1 HCV: 38.1 vs 33.4 HBV + HCV: 9.1 vs 7.8 Other: 4.1 vs 11.7	Child-Pugh: A: 73.3 vs 62.4 B: 23.9 vs 30.4 C: 2.8 vs 7.2 (p<0.001)	BCLC, p<0.001: Very early: 8.2 vs 6.5 Early: 60.4 vs 23.1 Intermediate: 21.7 vs 35.2 Advanced: 6.9 vs 30.9 Terminal: 2.8 vs 7.1	Resection: 23.9 vs 17.0 RFA: 12.6 vs 3.2 PEI: 9.1 vs 2.5 TACE: 47.2 vs 38.2 chemotherapy or radiation: 1.6 vs 12.3 None: 5.6 vs 26.7 (p<0.001)	Unadjusted HR 0.43 (95% CI 0.37-0.52) Median survival (m) 48.1 vs 12.7 Survival (%) at 3yr: 59.1 vs 29.3 (p<0.001)	Adjusted[e] HR 0.83 (95% CI 0.67-1.0)
Leykum, 2007[39] US. Michael DeBakey VAMC, Houston TX 2000-2005	2 AFP levels or one US/CT each year prior to diagnosis 16 vs 56	age: 59 vs 53.8 white: 64.2 vs 33.9	HBV: 40 vs 40 HCV: 100 ETOH: 0.68 vs 13.6	Child-Pugh: 6.3 vs 7.2	BCLC early: 100 vs 22, p<0.001	Resection: 6.3 vs 0 OLT: 6.3 vs 0 RFA: 50 vs 10.7	Unadjusted HR 0.27 (95% CI 0.13-0.60) Mean survival (m) 19.8 vs 8.5	Adjusted[f] HR 1.01 (95% CI 0.33-3.07)
Pascual, 2008[40] Europe: Spain 1996-2005	US+AFP, 6 117; NA	age: 68.8 vs 68.2 male: 66 vs 81 (p=0.002)	HBV: 3 vs 6 HCV: 61 vs 35 EtOH: 21 vs 35 EtOH + virus: 5 vs 11 (p<0.001)	Child-Pugh: A: 64 vs 33 B: 27 vs 48 C: 9 vs 19 (p<0.001)	<5cm: 60 vs 33 >5cm: 9 vs 28 multifocal: 14 vs 32 (p=0.003)	OLT: 15 vs 3 PEI: 19 vs 9 RF: 13 vs 4 TACE: 39 vs 20 none: 14 vs 64 (p<0.001)	Median survival (m) 27 vs 6 (p=0.001)	Adjusted HR[g] 0.4 (0.3-0.6), p=0.00003)
Tanaka, 2006[41] Asia: Japan 1991-2003	US+AFP, 6 182 vs 202	male: 60 vs 78	HCV: 100	Child-Pugh: A: 64 vs 58 B: 32 vs 39 C: 3 vs 3	Milan: 86 vs 50	Resection: 16 vs 12 PEI/RFA: 60 vs 34 TACE: 20 vs 42 Chemotherapy: 3 vs 9 (p<0.001)	Median survival (y) 4.7 vs 3.1 (p<0.001) Survival (%) at 3yr: 67 vs 51 5yr: 46 vs 32	Adjusted[h] RR 0.63 (95%CI 0.48–0.82). Corrected for lead time, survival was longer with screening among Child–Pugh class A patients when assumed tumor doubling time was ≤120 days: 60 days (p=0.005) 90 days (p=0.016) 120 days (p=0.048) 150 days (p=0.129) 180 days (p=0.293)

Author, Year, Setting, Years of enrollment	Screening modality, frequency (months); N screening vs no screening	Demographics (age; % male; race) Etiology, %	Etiology, %	Liver disease severity, %	Stage at Diagnosis, %	Treatment received, %	Observed mortality, screening vs no screening	Adjusted mortality, screening vs no screening
Taura, 2005[42] Asia: Japan 1991 – 2001	US, 3-12 AFP+liver function tests, 3-6 178 vs 93	age: 64.9 vs 64.3 male: 71.3 vs 85.0	HBV: 15.8 vs 15.0 HCV: 74.7 vs 69.9 HBV + HCV: 3.9 vs 1.1 Alcohol: 1.7 vs 4.3	Child-Pugh: A: 69.7 vs 74.2 B: 24.2 vs 20.4 C:6.1 vs 5.4	<3 cm: 64.6 vs 22.6 <5 cm: 94.4 vs 51.6 >3 tumors: 24.7 vs 45.2	Resection: 2.8 vs 3.2 RFA/PEI: 48.3 vs 17.2, p<0.0001 TACE:41.0 vs 59.2, (p=0.01)	Median survival overall (m): 37.3. Cumulative survival was significantly higher in screening vs no screening, NOS (p=0.01)	*
Tong, 2010[43] U.S. Pasadena, CA 1991-2008	US+AFP, 6 (cirrhosis, chronic liver disease) US+AFP, 12 (inactive carriers) 26 vs 52	age: 61.5 vs 52.9 (p=0.009) male: 80.8 vs 82.6	HBV: 100	Child-Turcott-Pugh: A: 65 vs 72.1 B: 25 vs 23.3 C: 10 vs 4.70	Milan: 61.5 vs 19.6, p=0.0004 UCSF: 76.9 vs 27.5, p<0.0001 tumors: Single: 81 vs 52 Multiple/diffuse: 19 vs 48 Metastasis: 7.7 vs 19.2 (p=0.02)	No screening vs screening: Resection: 19.2 vs 17.3 OLT: 30.1 vs 5.8 RFA and/or TACE: 26.9 vs 23.1 Chemotherapy: 0 vs 9.6 Supportive care: 23.1 vs 44.2 (p=0.012)	Survival (%) at 1yr: 100 vs 76.9 3yr: 62.5 vs 36.6 5yr: 35.7 vs 16.3 (p=0.007)	Adjusted[i] HR was non-significant, NOS. A lead time bias interval was added to the survival time of patients who presented with HCC, with tumor doubling time assumed to be 216 days.
Trevisani, 2002[44] Europe: Italy 1988-1998	US+AFP, 6 Group 1: semiannual screening, Group 2: annual screening Group 3: symptoms or incidental diagnosis 215 (group 1) vs 155 (group 2) vs 451 (group 3)	male: 70.7 vs 71 vs 78.7 (p=0.03)	HBV: 13.6 vs 20.4 vs 20.5 HCV: 66.6 vs 62.5 vs 55.9 HBV+HCV: 9.9 vs 9.9 vs 8.4 EtOH:8.5 vs 7.2 vs 13.8	Child-Pugh: A: 63.7 vs 70.9 vs 54 B: 30.7 vs 23.7 vs 33.8 C: 5.6 vs 5.4 vs 12.2 (p=0.001)	Milan: 68.7 vs 60.4 vs 31 (p<0.001)	OLT: 3.9 vs 0.2 resection: 11.6 vs 8.2 PEI: 26 vs 18.7 TACE: 33.4 vs 27.3 (p<0.001)	Median survival (m) 36 vs 34 vs 14 (p<0.001)	Adjusted[j] RR for Child-Pugh A subgroup: 0.59 (95% CI 0.45-0.78). Survival corrected for lead time was NS higher with screening in Child-Pugh B (p=0.051) and C subgroups (p=0.49).
Trevisani, 2004[45] Europe: Italy 1988-2001	Group 1: US+AFP, 6-12 Group 2: incidental diagnosis Group 3: symptoms 158 (group 1 vs 138(group 2) vs 67 (group 3)	age: 73.9 vs 74.9 vs 74.6 male: 60.8 vs 68.8 vs 76.1 (p=0.04)	HBV: 9.5 vs 6.5 vs 11.9 HCV: 67.1 vs 58.0 vs 53.7 HBV+HCV: 2.5 vs 3.6 vs 7.5 EtOH:5.7 vs 12.3 vs 10.4 EtOH+viral: 10.8 vs 10.9 vs 7.5	Child-Pugh: A: 76.8 vs 68.7 vs 42.4 B: 18.8 vs 29.8 vs 43.9 C: 4.6 vs 1.5 vs 13.6 (p<0.001)	Milan: 70.3 vs 39.1 vs 25.4 (p<0.001)	Resection: 8.4 vs 2.9 vs 0 PEI: 35.7 vs 36.8 vs 10.8 TACE: 28.6 vs 17.6 vs 20 Other/palliation: 27.3 vs 42.6 vs 69.2 (p<0.001)	Median survival (m) 30 vs 21(p=0.006) v 7 (p<0.001)	*

Author, Year, Setting, Years of enrollment	Screening modality, frequency (months); N screening vs no screening	Demographics (age; % male; race) Etiology, %	Etiology, %	Liver disease severity, %	Stage at Diagnosis, %	Treatment received, %	Observed mortality, screening vs no screening	Adjusted mortality, screening vs no screening
Wong, 2008[46] Asia: China (Hong Kong) 2003-2005	AFP, 6 US, 12-24 79 vs 393	age: 59.5 vs 58.7 male: 70 vs 88	overall HBV: 91 HCV: 10	Mean child-Pugh: 6.0 vs 6.4 (p=0.02)	Mean tumor, n: 2.6 vs 3.8 (p=0.03) Median tumor diameter (cm): 4.2 vs 7.7 (p<0.001) Extrahepatic metastasis: 8 vs 23 (p=0.002) Portal vein thrombosis: 11 vs 30 (p=0.001) Bilobal involvement: 14 vs 31 (p=0.01)	Resection: 20 vs 10, p=0.01 Transplant: 1 vs 1 Chemotx:13 vs 15 Local ablative tx: 46 vs 19, p<0.001	Median survival (wk) 88 vs 26 (p<0.001) Survival (%) at 1yr: 65.6 vs 35.5 2yr: 49.4 vs 21.1	Adjusted[k] HR 0.66 (95% CI 0.48-0.92) Survival (%) at 2yr: 49.4 in the screening group; correcting for lead-time bias in the non-screening group, by tumor doubling time: 26.7 (p=0.0035) 60-day 28.6 (p=0.035) 90-day 32.2 (p=0.18) 120-day
Yu, 2004[47] Asia: Taiwan 1996-1997	US, NR 164 vs 516	age % ≥50: 73.8 vs 65.9 male: 73.2 vs 79.3	HBV: 67.7 vs 53.57 HCV: 43.9 vs 31.3	Cirrhosis: 91.9 vs 68.2, Ascites: 10.1 vs 21.9	TNMS I: 66.2 vs 19.3 II: 27.2 vs 37.2 III: 3.7 vs 28.9 IV: 2.9 vs 14.6 (p<0.0001)	Hepatic resection: 53.5 vs 34 (p<0.0001) TACE: 35.1 vs 29.9	Unadjusted OR (95% CI) of survival at 1yr: 3.57 (5.26–2.38) 2yr: 3.70 (5.26–2.56) 3yr: 3.57 (5.26–2.44)	Adjusted[l] OR (95% CI) of survival at 1yr: 1.72 (2.86–1.03) 2yr: 2.22 (3.70-1.35) 3yr: 2.27 (3.85–1.37)

Abbreviations: (m) = months; NOS = not otherwise specified; NS = nonsignificant(ly).
* Potentially confounding variables were examined but an adjusted hazard ratio was not reported.
Confounders adjusted for in analysis:
[a] Age, sex, HBV, AST, AFP
[b] Screening test in the 3-6 years before HCC, year of diagnosis, age, race, MELD, psychosis, ascites, varices, encephalopathy
[c] Receipt of therapy, number of lesions, Child-Pugh
[d] Disease severity, cause, renal function, alcohol use, stage
[e] Etiology of disease, AFP level, solitary tumor, absence of portal vein thrombus, stage, surgical resection
[f] Psychiatric disease, PCP at tertiary center, hepatology assessment before diagnosis, early stage, receipt of potentially curative treatment.
[g] Child–Pugh status, tumor characteristics, treatment received
[h] AFP, Child-Pugh
[i] Single tumors, UCSF criteria, CTP class A, platelets per log10 increase, AST per log10 increase
[j] Sex, HBV, AFP
[k] Age, sex, and Child-Pugh
[l] Age, HBV, HCV, cirrhosis, ascites, ALT, AFP, and lead time adjustment.