評価対象論文リスト（要因：①B型・C型肝炎ウイルス感染、②C型慢性肝炎抗ウイルス療法、アウトカム：肝がん）

評価判定日：2024/12/23

①既存の系統的レビュー・メタ解析・統合解析

1	Akita T, Tanaka J, Satake M, et al. Meta-regression Analysis of Sex- and Birth Year-Specific Prevalence of HBsAg and Anti-HCV Among Un-diagnosed Japanese: Data From the First-time Blood Donors, Periodical Health Checkup, and the Comprehensive Health Checkup With Lifestyle Education (Ningen Dock). *J Epidemiol* . 2020;30(9):420-425. doi:10.2188/jea.JE20190055	B型・C型肝炎ウイルスの保有率に関する研究
2	Yamagiwa Y, Tanaka K, Matsuo K, et al. Response to antiviral therapy for chronic hepatitis C and risk of hepatocellular carcinoma occurrence in Japan: a systematic review and meta-analysis of observational studies. C and risk of hepatocellular carcinoma occurrence in Japan: a systematic review and meta-analysis of. In Japan: a systematic review and metat Y Rep. 2023;13(3):3899-386. doi:10.1038/s41598-023-31052-6	C型慢性肝炎ウイルス治療

②日本人個別研究（ランダム化比較試験、コホート研究、症例対照研究、横断研究などの個別疫学研究）

3	Nishioka K, Levin AG, Simons MJ. Hepatitis B antigen, antigen subtypes, and hepatitis B antibody in normal subjects and patients with liver disease. Bull World Health Organ. 1975;52(3):293-300.	B型・C型肝炎ウイルス感染
4	Kubo Y, Okuda K, Hashimoto M, Nagasaki Y, Ebata H. Antibody to hepatitis B core antigen in patients with hepatocellular carcinoma. Gastroenterology. 1977;72(6):1217-1220.	B型・C型肝炎ウイルス感染
5	Akagi G, Furuya K, Otsuka H. Hepatitis B antigen in the liver in hepatocellular carcinoma in Shikoku, Japan. Cancer. 1982;49(4):678-682. doi:10.1002/1097-0142(19820215)49:4<678::aid-cncr2820490416>3.0.co;2-f	B型・C型肝炎ウイルス感染
6	Inaba Y, Maruchi N, Matsuda M, Yoshihara N, Yamamoto S. A case-control study on liver cancer with special emphasis on the possible aetiological role of schistosomiasis. Int J Epidemiol. 1984;13(4):408-412. doi:10.1093/ije/13.4.408	B型・C型肝炎ウイルス感染
7	Oshima A, Tsukuma H, Hiyama T, Fujimoto I, Yamano H, Tanaka M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. Int J Cancer. 1984;34(6):775-779. doi:10.1002/ijc.2910340607	B型・C型肝炎ウイルス感染
8	深尾 彰, B型肝炎ウイルスと肝細胞癌との関連性に関する疫学的研究, 日本消化器病学会雑誌, 1985, 82 巻, 2 号, p. 232-238, 公開日 2007/12/26, Online ISSN 1349-7693, Print ISSN 0446-6586, https://doi.org/10.11405/nisshoshi1964.82.232, https://www.jstage.jst.go.jp/article/nisshoshi1964/82/2/82_2_232/_article/-char/ja	B型・C型肝炎ウイルス感染
9	平賀正治, 荒木俊一, 寺尾英夫, 村田勝敬, 横山和仁. 日本人の肝細胞癌に及ぼすHBs抗原および飲酒の影響とその相互作用の解析. 日本公衛誌. 1986	B型・C型肝炎ウイルス感染
10	Tamura I, Kurimura O, Inaba Y. A follow-up study of hepatitis B virus carriers at hospital. Jpn J Cancer Res. 1986;77(10):992-997.	B型・C型肝炎ウイルス感染
11	Tokudome S, Ikeda M, Matsushita K, Maeda Y, Yoshinari M. Hepatocellular carcinoma among female Japanese hepatitis B virus carriers. Hepatogastroenterology. 1987;34(6):246-248.	B型・C型肝炎ウイルス感染
12	Sakuma K, Saitoh N, Kasai M, et al. Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. Hepatology. 1988;8(6):1642-1646. doi:10.1002/hep.1840080628	B型・C型肝炎ウイルス感染

13	Tokudome S, Ikeda M, Matsushita K, Maeda Y, Yoshinari M. Hepatocellular carcinoma among HBsAg positive blood donors in Fukuoka, Japan. Eur J Cancer Clin Oncol. 1988;24(2):235-239. doi:10.1016/0277-5379(88)90259-3	B型・C型肝炎ウイルス感染
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17	Fukuda K, Shibata A, Hirohata I, Tanikawa K, Yamaguchi G, Ishii M. A hospital-based case-control study on hepatocellular carcinoma in Fukuoka and Saga Prefectures, northern Kyushu, Japan. Jpn J Cancer Res. 1993;84(8):708-709. doi:10.1111/j.1349-7006.1993.tb02033.x	B型・C型肝炎ウイルス感染
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51	Kobayashi, S. et al.. Development of hepatocellular carcinoma in patients with chronic hepatitis C who had a sustained virological response to interferon therapy: A multicenter, retrospective cohort study of 1124 patients. Liver Int.. 2007;27(2):186-189. doi:https://doi.org/10.1111/j.1478-3231.2006.01406.x	C型慢性肝炎ウイルス治療
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（HBV、HCV感染）

Reference			Study subjects						Category	Number among cases	Relative risk (95%CI or p)	P for trend	Confounding variables considered	**Magnitude of association**
Author	Title	Year	Study period	Number of subjects	Source of subjects	Event followed	Number of incident cases or	Participant's race						
Ishiguro et al	Impact of viral load of hepatitis C on the incidence of hepatocellular carcinoma: A population-based cohort study (JPHC Study)	2011	BL: 1993-1994 FLW: 2005	20,794 men; 7,517 women; 13,277	JPHC Study	Hepatocellular carcinoma incidence	114	Japanese	HVC(-), HBV(-) HVC(+), HBV(-) HVC(-), HBV(+) HVC(+), HBV(+) HVC(+) and/or HBV(+)	24 76 12 2 90	1.0 (Reference) 35.8 (20.4, 62.7) 16.1 (7.6, 33.9) 46.6 (10.6, 205.1) 28.2 (17.0, 46.6)	N/A	age, study area, weekly ethanol intake, body mass index, alanine aminotranserase level, coffee intake	↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑

（C型慢性肝炎ウイルス：コホート研究、アウトカムはいずれも肝がん）

Reference			Study subjects						Category	Number among cases	Relative risk (95%CI or P)	P for trend	Confounding variables considered	**Magnitude of association**	Comments
Author	Title	Year	Study period	Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths	Participant's race							
Ikeda et al	A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis	1993	1974-1989?	588 (415 men and 173 women) (age 19-84)	Patients with viral or alcoholic cirrhosis at Toranomon Hospital, Tokyo	Incidence	185	Japanese	Serum anti-HCV Negative Positive	 31 154	 1.0 2.4 (1.4 - 4.1)	N/A	Age, alpha-fetoprotein, drinking, ICG R15	↑ ↑ ↑	Second generation ELISA was used for anti-HCV detection.
Tsukuma et al	Risk factors for hepatocellular carcinoma among patients with chronic liver disease	1993	1987-1991	917 (548 men and 369 women) (age 40-69)	Patients with chronic hepatitis or compensated cirrhosis at Center for Adult Diseases, Osaka	Incidence	54	Japanese	Serum anti-HCV Negative Positive	 	 1.0 4.1 (1.3 - 12.9)	N/A	Age, sex, stage of disease, alpha-fetoprotein, HBsAg, anti-HBc, smoking, drinking	↑ ↑ ↑	First generation ELISA (C100-3 antibody) was used for anti-HCV detection.
Kato et al	Risk of hepatocellular carcinoma in patients with cirrhosis in Japan	1994	1977-1993	255 (173 men and 82 women) (age 22-83)	Patients with compensated cirrhosis in Nagasaki prefecture	Incidence	96	Japanese	Serum hepatitis virus marker anti-HCV(-) HBsAg(-) anti-HCV(+) HBsAg(-) anti-HCV(-) HBsAg(+) anti-HCV(+) HBsAg(+)	 4 55 33 4	 1.0 3.5 (1.4 - 8.9) 3.0 (1.2 - 7.9) 3.2 (1.0 - 10.5)	N/A	None	 ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑	Second generation enzyme immunoassay or radioimmunoassay was used for anti-HCV detection. The relative risks were not described in the original paper, and were estimated by one of the authors (KT).
Tanaka et al	A long-term follow-up study on risk factors for hepatocellular carcinoma among Japanese patients with liver cirrhosis	1998	1985-1995	72 (46 men and 26 women) (age 40-69)	Patients with liver cirrhosis at Kyushu University Hospital	Incidence	26 (19 men and 7 women)	Japanese	Serum anti-HCV Negative Positive	 2 24	 1.0 3.4 (0.6 - 20.0)	N/A	Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST, alpha-fetoprotein, HBsAg	↑ ↑ ↑	Second generation immunoradiometric and recombinant immunoblot assays were used for anti-HCV detection. The relative risk was not described in the original paper, and was reestimated by one of the authors (KT).
Iida et al	Chronic Japanese schistosomiasis and hepatocellular carcinoma: ten years of follow-up in Yamanashi Prefecture, Japan	1999	1985-1996	218 (sex and age not specified)	Patients with chronic schistosomias is or chronic	Incidence	37	Japanese	Serum anti-HCV Negative Positive	 9 28	 1.0 3.2 (1.6 - 6.4)	N/A	None	↑ ↑ ↑	Second generation passive hemagglutination was used for anti-HCV detection. The relative risk was not

					liver disease in Yamanashi prefecture										described in the original paper, and was estimated by one of the authors (KT).
Boschi-Pinto et al.	A follow-up study of morbidity and mortality associated with hepatitis C virus infection and its interaction with human T lymphotropic virus type I in Miyazaki, Japan	2000	1984-1997	965 (389 men and 576 women) (age not specified)	Residents in a village in Miyazaki prefecture	Death	8	Japanese	Serum anti-HCV Negative Positive	 2 6	 1.0 8.2 (1.6 - 41.4)	N/A	Sex, age, smoking, drinking, hymant T lymphotropic virus	 ↑ ↑ ↑	Second generation particle agglutination and recombinant immunoblot assays were used for anti-HCV detection.
Mori et al	Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan	2000	1992-1997	3052 (974 men and 2078 women) (age >= 30)	Residents in a town in Saga prefecture	Incidence	22 (14 men and 8 women)	Japanese	Serum anti-HCV Negative Positive, low titier Positive, high titer	 3 1 18	 1.0 3.4 (0.4 - 33.5) 40.4 (11.7 - 139.2)	N/A	Sex, age	 ↑ ↑ ↑ ↑ ↑ ↑	Second generation passive hemagglutination was used for anti-HCV detection.
Nagao et al	A cohort study of chronic liver disease in an HCV hyperendemic area of Japan: a prospective analysis for 12 years	2004	1990-2002	509 (217 men and 292 women) (age 20-94)	Randomly selected inhabitants in a town in Fukuoka prefecture	Death	9 (6 men and 3 women)		Serum anti-HCV Negative Positive	 1 8	 1.0 26.5 (2.9 - 239.8)	N/A	Serum HBsAg	 ↑ ↑ ↑	The relative risk was not described in the original paper, and was estimated by one of the authors (KT), based on the Mantel-Haenszel method.

(B型慢性ウイルス肝炎：コホート研究、アウトカムはいずれも肝がん)

Reference			Study subjects						Category	Number among cases	Relative risk (95%CI or P)	P for trend	Confounding variables considered	**Magnitude of association**	Comments
Author	Title	Year	Study period	Number of subjects for analysis	Source of subjects	Event followed	Number of incident cases or deaths	Participant's race							
Oshima et al	Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer	1984	1972-1980	8646 men (age 15-64)	HBsAg-positive blood donors at Osaka Red Cross Blood Center	Incidence Death	20 men	Japanese	Serum HBsAg Positive	 20	O/E ratio 6.6 (4.0 - 10.2) 7.8 (4.8 - 12.0)		Age, observation period	↑ ↑ ↑ ↑ ↑ ↑	Electrosyneresis was used for HBsAg detection.
Fukao	[An epidemiological study on relationship between hepatitis B virus and hepatocellular carcinoma]	1984	1971-1980	11000 men (age 30-64)	Blood donors in Miyagi prefecture	Incidence	4 men	Japanese	Serum HBsAg Negative Positive	 1 3	 1.0 30.0 (3.1 - 288.4)		Age, residence, time of blood donation	 ↑ ↑ ↑	Electrosyneresis was used for HBsAg detection.
Tamura et al	A follow-up study of hepatitis B virus carriers at hospital	1986	1970-1984	178523 (81404 men and 97119 women) (age 0-89)	Patients at Kure National Hospital	Death	298 (223 men and 75 women)	Japanese	Serum HBsAg, men Negative Positive Serum HBsAg, women Negative Positive Serum HBsAg, men Positive Serum HBsAg, women Positive	 171 52 56 19 52 19	 1.0 26.9 (19.9 - 36.4) 1.0 46.5 (27.8 - 77.8) O/E ratio 83.9 (62.6 - 110) O/E ratio 190.0 (114 - 297)		None None Age, observation period Age, observation period	 ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑	Reversed passive hemagglutination was used for HBsAg detection.
Tokudome et al	Hepatocellular carcinoma among female Japanese hepatitis B virus carriers	1987	1977-1985	3769 women (age not specified)	HBsAg-positive blood donors at Fukuoka Red Cross Blood Center	Death	4 women	Japanese	Serum HBsAg Positive	 4	O/E ratio 5.6 (1.5 - 14.4)		Age, observation period	 ↑ ↑ ↑	Electrosyneresis and reverse passive hemagglutination were used for HBsAg detection.

Tokudome et al	Hepatocellular carcinoma among female Japanese hepatitis B virus carriers	1988	1977-1983	2595 men (age not specified)	HBsAg-positive blood donors at Fukuoka Red Cross Blood Center	Death	15 men	Japanese	Serum HBsAg Positive	15	O/E ratio 7.2 (4.1 - 12.0)	Age, observation period	↑ ↑ ↑	Electrosyneresis and reversed passive hemagglutination were used for HBsAg detection.
Sakuma et al	Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study	1988	1977-1985	25547 men (age 40, 45, 50 and 55)	Employees of Japan National Railways	Death	30 men	Japanese	Serum HBsAg Negative Positive	21 9	1.0 20.9 (9.6 - 45.4)	None	↑ ↑ ↑	Reversed passive hemagglutination was used for HBsAg detection. The relative risk was not described in the original paper, and was reestimated.
Inaba et al	肝硬変から肝がんへのプロセスにおける飲酒・喫煙習慣の影響	1990	1973-1988	270 men (age 26-75)	Patients with liver cirrhosis at Juntendo University Hospital	Death	46 men	Japanese	Serum HBsAg Negative		1.00	Age, histories of transfusion, hepatitis and surgical operation, drinking, smoking		
Kato et al	The risk and predictive factors for developing liver cancer among patients with decompensated liver cirrhosis	1992	1987-1990	777 (age >= 16)	Patients with decompensated liver cirrhosis or post-transfusion hepatitis	Incidence	74	Japanese	Serum HBsAg Negative Positive	58 16	1.0 1.8 (1.0 - 3.3)	Sex, age, ALT, alpha-fetoprotein, drinking, HBeAg	↑ ↑ ↑	
Ikeda et al	A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis	1993	1974-1989	588 (415 men and 173 women) (age 19-84)	Patients with viral or alcoholic cirrhosis at Toranomon Hospital, Tokyo	Incidence	185	Japanese	Serum HBsAg Negative Positive	147 38	1.0 0.66 (0.38 - 1.17)	Age, alpha-fetoprotein, drinking, ICG R15	↓	Radioimmunoassay was used for HBsAg detection.
Tsukuma et al	Risk factors for hepatocellular carcinoma among patients with chronic liver disease	1993	1987-1991	917 (548 men and 369 women) (age 40-69)	Patients with chronic hepatitis or compensated cirrhosis at Center for Adult Diseases, Osaka	Incidence	54	Japanese	Serum HBsAg Negative Positive		1.0 6.9 (2.9 - 16.4)	Age, sex, stage of disease, alpha-fetoprotein, anti-HBc, anti-HCV, smoking, drinking	↑ ↑ ↑	Reversed passive hemagglutination was used for HBsAg detection.
Kato et al	Risk of hepatocellular carcinoma in patients with cirrhosis in Japan	1994	1977-1993	255 (173 men and 82 women) (age 22-83)	Patients with compensated cirrhosis in Nagasaki prefecture	Incidence	96	Japanese	Serum hepatitis virus marker HBsAg(-) anti-HCV(-) HBsAg(+) anti-HCV(-) HBsAg(-) anti-HCV(+) HBsAg(+) anti-HCV(+)	4 33 55 4	1.0 3.0 (1.2 - 7.9) 3.5 (1.4 - 8.9) 3.2 (1.0 - 10.5)	None	↑ ↑ ↑ ↑ ↑ ↑	Radioimmunoassay was used for HBsAg detection. The relative risks were not described in the original paper, and were estimated by one of the authors (KT).
Tanaka et al.	Hepatitis C virus infection and risk of hepatocellular carcinoma among Japanese: possible role of type 1b (II) infection	1998	1985-1995	72 (46 men and 26 women) (age 40-69)	Patients with liver cirrhosis at Kyushu University Hospital	Incidence	26 (19 men and 7 women)	Japanese	Serum HBsAg Negative Positive	25 1	1.0 0.32 (0.03 - 3.60)	Sex, age, years since LC diagnosis, department, hospitalization status, serum albumin, AST,	↓ ↓	Reversed passive hemagglutination was used for HBsAg detection. The relative risk was not described in the original paper, and was

													alpha-fetoprotein, anti-HCV	reestimated by one of the authors (KT).
Iida et al	Chronic Japanese schistosomiasis and hepatocellular carcinoma: ten years of follow-up in Yamanashi Prefecture, Japan	1999	1985-1996	100 (sex and age not specified)	Anti-HCV-negative patients with chronic schistosomiasis or chronic liver disease in Yamanashi prefecture	Incidence	9	Japanese	Serum HBsAg Negative Positive	 5 4	 1.0 1.6 (0.5 - 5.7)		None	Enzyme immunoassay was used for HBsAg detection. The relative risk was not described in the original paper, and was estimated by one of the authors (KT). ↑
Mori et al	Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption, and other factors associated with hepatocellular carcinoma risk in Japan	2000	1992-1997	3052 (974 men and 2078 women) (age >= 30)	Residents in a town in Saga prefecture	Incidence	22 (14 men and 8 women)	Japanese	Serum HBsAg Negative Positive	 20 2	 1.0 7.3 (1.6 - 32.6)		Sex, age	 ↑ ↑ ↑
Nagao et al	A cohort study of chronic liver disease in an HCV hyperendemic area of Japan: a prospective analysis for 12 years	2004	1990-2002	509 (217 men and 292 women) (age 20-94)	Randomly selected inhabitants in a town in Fukuoka	Death	9 (6 men and 3 women)	Japanese	Serum HBsAg Negative Positive	 8 1	 1.0 4.9 (0.5 - 43.8)		Serum anti-HCV	 ↑ ↑	The relative risk was not described in the original paper, and was estimated by one of the authors (KT), based on the Mantel-

（HCV治療）

Reference			Include study					Design	Category	Relative risk (95% CI or p)	Weight	**Magnitude of association**
Author	Title	Year	Ref No.	First author	Year	Study period	Study location	Event (*Definition)					
Yamagiwa Y, Tanaka K, Matsuo K, et al.	Response to antiviral therapy for chronic hepatitis C and risk of hepatocellular carcinoma occurrence in Japan: a systematic review and meta-analysis of observational studies	2023	46	Umehara Y	2017	2004-2014	Japan	Hepatocellular carcinoma incidence	Retrospective hospital-based single	SVR (sustained virologic response) vs. non-SVR	0.38 (0.15, 0.99)	8.61	
			49	Honda T	2015	2004-2010	Japan		Retrospective hospital-based multi		0.21 (0.10, 0.45)	13.03	
			50	Oze T	2014	2002-2008	Japan		Prospective hospital-based multi		0.37 (0.18, 0.74)	14.85	
			44	Arase Y	2013	1990-2009	Japan		Retrospective hospital-based single		0.20 (0.15, 0.28)	41.86	
			52	Osaki Y	2012	2002-2010	Japan		Retrospective hospital-based single		0.12 (0.02, 0.94)	1.97	
			54	Takahashi H	2011	2002-2007	Japan		Retrospective hospital-based single		0.05 (0.01, 0.48)	1.62	
			55	Asahina Y	2010	1992-2008	Japan		Prospective hospital-based multi		0.38 (0.18, 0.82)	12.77	
			56	Kurokawa M	2009	2002-2005	Japan		Retrospective blood donation/hospital-based		0.28 (0.08, 0.97)	5.29	
										Overall	0.25 (0.19, 0.34)	100	↓ ↓ ↓

Source: Figure 2. Forrest plot of the pooled estimate of the hazard ratio of HCC incidence adjusted for potential covariates in patients treated with antiviral therapy (SVR vs. non-SVR) in 8 studies.